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RESEARCH ARTICLE

Intraoperative Low-frequency Electroacupuncture under General Anesthesia Improves Postoperative Recovery in a Randomized Trial

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Abstract
Neuronal stimulation improves physiological responses to infection and trauma, but the clinical potential of this strategy is unknown. We hypothesized that transdermal neural stimulation through low-frequency electroacupuncture might control the immune responses to surgical trauma and expedite the postoperative recovery. However, the efficiency of electroacupuncture is questioned due to the placebo effect. Here, electroacupuncture was performed on anesthetized patients to avoid any placebo. This is a prospective double-blinded pilot trial to determine whether intraoperative electroacupuncture on anesthetized patients improves postoperative recovery. Patients with electroacupuncture required 60% less postoperative analgesic, even they had pain scores similar to those in the control patients. Electroacupuncture prevented postoperative

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hyperglycemia and attenuated serum adrenocorticotropic hormone in the older and heavier group of patients. From an immunological perspective, electroacupuncture did not affect the protective immune responses to surgical trauma, including the induction of interleukin-6 and interleukin-10. The most significant immunological effect of electroacupuncture was enhancing transforming growth factor-β1 production during surgery in the older and lighter group of patients. These results suggest that intraoperative electroacupuncture on anesthetized patients can reduce postoperative use of analgesics and improve immune and stress responses to surgery.

Introduction

The Centers for Disease Control and Prevention estimates that there are over 51 million surgical procedures performed annually in the USA. Over 85% of surgical patients report significant postoperative pain, with a higher incidence in female patients [1]. Postoperative pain is treated with opioids that have multiple adverse side effects including respiratory depression and decreased intestinal motility [2]. These side effects increase the risk of surgical complications and delay postoperative recovery [3,4]. Furthermore, surgical trauma induces hyperglycemia, physiological stress, and inflammation that can cause cardiovascular, renal, and neurological complications contributing to postoperative mortality [5–7]. Postoperative hyperglycemia is an insulin resistance process that exacerbates inflammation, delays wound healing, and infections. Therefore, there is a clinical need of novel strategies to reduce hyperglycemia and improve postoperative recovery.

Neuromodulation represents efficient systems selected by evolution to control physiological homeostasis [8–10]. Thus, neural stimulation can be a promising strategy to attenuate surgical trauma. We reported that electrical stimulation of the vagus nerve improves physiological responses to infection and trauma [9,10]. These results were confirmed by other investigators reporting that vagal stimulation improved physiological responses to experimental ischemia and reperfusion, hemorrhage, resuscitation, pancreatitis, colitis, endotoxemia, septic shock, and severe sepsis [9–12]. In humans, surgical implantation of vagus nerve stimulators was first approved by the Food and Drug Administration in 1997 for the treatment of refractory epilepsy [13]. However, these studies have limited clinical implications because they were performed through a surgical stimulation of the vagus nerve. Recently, we reported that transdermal neuronal stimulation with electroacupuncture (EA) also regulates physiological responses to infection and trauma [9]. Thus, transdermal neuronal stimulation with EA can represent a promising clinical approach to alleviate surgical trauma and improve postoperative recovery.

EA is currently endorsed by the National Institutes of Health and the World Health Organization. Previous studies analyzed the potential of EA to alleviate postoperative pain and nausea [14–16]. However, the results from these studies were contradictory [16]. Many investigators question these results because the patients were conscious and therefore susceptible to placebo [14,15,17–19]. Indeed, many clinical studies on EA were not conclusive as the results were statistically similar to the placebo group [18,20]. We recently reported that EA regulated physiological responses to infection and trauma in anesthetized mice [9], which are not susceptible to the placebo effect. Similar studies also indicated that ST36 stimulation induced antinociceptive effects via adenosine A1 receptors [17]. The use of EA on anesthetized patients has been previously avoided assuming that general anesthesia may conceal the analgesic effects of EA. We hypothesized that low-frequency EA may prevent physiological stress and improve postoperative recovery. Low frequency EA acts on the arcuate nucleus of the hypothalamus, and converges in the periaqueductal grey matter to induce endomorphin/beta-endorphin/encephalin. The effects of endomorphin/beta-endorphin/encephalin in low-frequency EA are mediated by the mu/delta opioid receptors [21]. Thus, low-frequency EA can induce analgesic effects that depend on the activation of the opioidergic system. Here we performed a prospective double-blinded randomized pilot study to determine whether intraoperative EA (using acupoints LI-4, LI-11, and ST-36) on anesthetized patients undergoing thyroid or parathyroid surgery could reduce the use of analgesic, pain score, physiological stress, or immune cytokine responses. Given that our previous studies indicated that EA inhibited the production of inflammatory cytokines [9], and surgical trauma induces inflammatory cytokines, we also analyzed whether intraoperative EA also regulated the immune cytokine responses.

Materials and methods

Clinical trial

A prospective pilot study approved by the Institutional Review Board (Pro2012002417) of the New Jersey Medical School, Rutgers University, Newark, NJ, USA and registered at clinicaltrials.gov (code NCT01937520). This was a prospective double-blinded study with 20 patients undergoing thyroid and parathyroid surgery randomized in two groups: EA ($n = 11$) group or sham (control, $n = 9$) group. Participation was voluntary without economical compensation, and each participant signed a written consent. Exclusion criteria include pre-existing diabetes, cardiovascular conditions, or elevated levels of blood glucose, insulin, or tumor necrosis factor (TNF). Patient #11 was excluded because of pre-existing levels of TNF > 1 ug/mL prior to surgery. All patients underwent the induction of anesthesia with midazolam

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