Use of Acupuncture in the Control of Chemotherapy-Induced Nausea and Vomiting

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Acupuncture, electroacupuncture, acupressure, electrostimulation, chemotherapy, nausea, vomiting, antiemetic

Abstract
Chemotherapy-induced nausea and vomiting (CINV) is one of the most common and feared side effects of chemotherapy. Despite recent advances in pharmacologic antiemetic therapy, additional treatment for breakthrough CINV is needed. Acupuncture is a safe medical procedure with minimal side effects; several randomized controlled clinical trials have suggested its efficacy in controlling this side effect. A recent meta-analysis of those trials demonstrated that acupuncture significantly reduced the proportion of patients experiencing acute chemotherapy-induced vomiting. Those trials, however, did not show that acupuncture significantly alleviated acute chemotherapy-induced nausea or delayed CINV. The clinical relevance of these results were limited by the fact that they predated the use of aprepitant and that only 1 or 2 acupuncture points were stimulated during acupuncture treatment. More clinical trials to study the effect of acupuncture with additional antiemetic acupuncture points in adjunct to modern pharmacologic antiemetic therapy are needed. (JNCCN 2009;7:606–612)

CINV Background
Before the advent of 5-hydroxytryptamine-3 (5-HT3)–receptor antagonists and neurokinin-1–receptor antagonists, CINV was poorly controlled. Among patients undergoing chemotherapy, 70% to 80% experienced severe CINV. Risk factors for CINV include female gender, young age, and treatment with highly emetogenic chemotherapy. Chemotherapy agents are divided into 4 emetogenic risk levels: high (> 90%), moderate (30%–90%), low (10%–30%), and minimal (< 10%). CINV can be either acute, delayed, or anticipatory. Acute CINV occurs within 24 hours of chemotherapy, usually beginning within 2 to 4 hours and peaking in the first 4 to 6 hours. Delayed CINV occurs from day 2 to 6 of chemotherapy. Anticipatory CINV occurs before chemotherapy treatments in patients who have previously experienced significant CINV. Most antiemetic research focuses on reducing acute and delayed CINV, with the understanding that this would result in better control of anticipatory CINV.
Mechanism of Action

Animal studies suggest that emetogenic chemotherapy agents entering the body through either mucosa or blood stimulate enteroendocrine cells located in the gastrointestinal mucosa of the proximal small intestine. Consequently, the enteroendocrine cells release local mediators, such as 5-HT, substance P, and cholecystokinin. These mediators then bind to the corresponding receptors at the end of the vagal afferent fibers located nearby, triggering the afferent stimuli and reaching the loosely organized neuronal areas within the medulla. Those neurons then coordinate the emetic reflex and result in nausea and vomiting.

Other studies suggest that CINV occurs after neurotransmitters, such as dopamine, 5-HT, or hormonal stimuli, bind to area postrema, a structure located in the caudal end of the fourth ventricle, or the limbic forebrain.

Pharmacologic Antiemetic Therapy

Corticosteroid has been used extensively as an antiemetic agent over the past 25 years, although its antiemetic mechanism is not well understood. Dopamine, 5-HT, and substance P are believed to be the important neurotransmitters mediating CINV. As a result, antiemetic medications are divided into 3 main categories: dopaminergic, 5-HT3-receptor, and neurokinin-1-receptor antagonists. Although dopaminergic antagonists, such as prochlorperazine, haloperidol, and metoclopramide, are the oldest and most widely used antiemetic drugs, they are associated with lower therapeutic index and greater potential side effects.

Understanding the important role 5-HT played in preventing CINV has revolutionized therapy; it has been regarded as the most important receptor in acute CINV. 5-HT3 receptors are located in both central (area postrema) and peripheral nervous systems (vagal afferents). Selective 5-HT3-receptor antagonists have been established as standard CINV prophylactic therapy for patients undergoing moderately or highly emetogenic chemotherapy. Common side effects associated with 5-HT3-receptor antagonists are mild headache, transient liver enzyme elevation, and constipation. Although 5-HT3-receptor antagonists are highly effective in preventing acute CINV, they have notably lower efficacy in preventing delayed CINV.

Substance P has also been suggested to play an important role in CINV. Its receptors, neurokinin-1 receptors, are located throughout central and peripheral nervous systems, including the area postrema and gastrointestinal tract. Aprepitant is the first drug in the class of neurokinin-1–receptor antagonists. Two phase III, randomized, controlled trials showed that the 3-drug combination of aprepitant, ondansetron, and dexamethasone controlled CINV significantly better than the 2-drug combination of ondansetron and dexamethasone during a 5-day study in patients undergoing highly emetogenic chemotherapy. These results led the FDA to approve adding aprepitant to antiemetic regimens for patients undergoing highly emetogenic chemotherapy.

Management

Based on available evidence, current antiemetic guidelines recommend a 3-drug combination of a 5-HT3–receptor antagonist, dexamethasone, and aprepitant for patients undergoing highly emetogenic chemotherapy. For moderately emetogenic chemotherapy, a 2-drug combination with a 5-HT3–receptor antagonist and dexamethasone is recommended. For low emetogenic chemotherapy, dexamethasone with or without dopaminergic antagonists is recommended. No antiemetic agent is recommended for chemotherapy agents with minimal emetic risk.

Using the current regimens, CINV is much less prevalent or severe. However, several questions remain. Although chemotherapy-induced vomiting has been much better controlled by the newly developed pharmacologic agents, chemotherapy-induced nausea is not. This problem was illustrated in a phase III, randomized, controlled trial assessing the role of aprepitant in patients receiving anthracycline and cyclophosphamide, in which aprepitant significantly lowered the proportion of patients experiencing chemotherapy-induced vomiting (76%–59%) but did not change the rate at which they experienced nausea. Lastly, even with the 3-drug regimen, 11% to 17% still experience acute CINV. Additional therapy is needed for breakthrough CINV and to better control nausea. Nonpharmacologic therapy, such as acupuncture, has therefore attracted significant research interest because of its minimal side effects and reported efficacies in relieving nausea and vomiting caused by multiple conditions.
Acupuncture

Acupuncture is a traditional Chinese medicine technique that involves inserting and manipulating filiform needles in predefined points on the skin (i.e., acupuncture points) to achieve therapeutic effect. It has been widely used in China to treat multiple medical conditions, such as pain, nausea, and vomiting. Acupuncture was introduced in the United States in 1971 after the New York Times reporter James Reaton reported that acupuncture relieved his postoperative pain after an emergency appendectomy while in Beijing. The use of acupuncture in controlling CINV was then acknowledged by the National Institutes of Health 1997 Consensus Statement, which claimed that promising research suggested that acupuncture was efficacious in reducing CINV. However, at that time, only 2 small clinical trials on acupuncture for controlling CINV had been published.

Although studies have not been able to fully explain the mechanism of acupuncture, experts have proposed that it works through its effect on neurotransmitters and neurohormones. Animal research suggests that acupuncture accomplishes its anesthetic effect by stimulating nerves in the muscle, which then relay the signal to the spinal cord, midbrain, and hypothalamus-pituitary system, which in turn lead to the release of neurotransmitters and hormones (i.e., endorphins and enkephalins). Acupuncture may work in a similar manner to relieve nausea and vomiting, although limited data are available to confirm this theory. In addition, modern human neuroimaging studies suggest that stimulating acupuncture points resulted in responses to the cortical and subcortical areas in the brain.

Deciding which acupuncture points to stimulate is the most important part of acupuncture treatment. More than 300 acupuncture points are located on the body and each point has its own therapeutic index. Picking the corresponding acupuncture points for specific medical conditions is critical. Multiple acupuncture points, such as pericardium 6 (P6), stomach 36 (ST36), stomach 44 (ST44), and convention vessel 12 (CV12), have been used to reduce nausea and vomiting in China. Acupuncture research on reducing nausea and vomiting, however, has primarily studied stimulating one acupuncture point: P6 (Neiguan in Chinese). P6 locates 3 fingers below the flexor crest and between the tendons of the flexor carpi radialis and palmaris longus.

Acupuncture points can be stimulated in various ways. With manual acupuncture, the filiform acupuncture needle is inserted in an acupuncture point and manually rotated to stimulate the point. With electroacupuncture, acupuncture points are stimulated by passing electrical current through inserted needles. Electrical current may also be passed through an electrode on the skin without inserting acupuncture needles, a technique called noninvasive electrostimulation. Acupressure is a form of modified acupuncture that replaces needles with physical pressure generated with either a finger or a device such as an embedded stud in an elastic wrist band.

Acupuncture Research

In 2005, Ezzo et al. published a comprehensive meta-analysis of 11 randomized clinical trials (N = 1247) evaluating the effect of acupuncture point stimulation in controlling CINV. Those trials were published between 1987 and 2003, and the sample sizes ranged from 10 to 747 patients. Among the 10 trials that reported chemotherapy regimen, all patients underwent moderately to highly emetogenic chemotherapy; 8 trials used a antiemetic regimen containing the 5-HT\_\_ receptor antagonist ondansetron, and the other 3 trials used methotrexate alone, methotrexate with prednisone, or methotrexate with dopaminergic antagonists. In addition, all of the antiemetic regimens predated aprepitant.

Four acupuncture point–stimulating modalities were used to control CINV: manual acupuncture, electroacupuncture, noninvasive acupuncture point stimulation, and acupressure. One trial with 80 patients examined the effect of manual acupuncture at P6. Three trials (N = 134) examined the effect of electroacupuncture on P6 (2 trials) and on P6 plus ST36 (1 trial). Four trials (N = 149) studied the effect of noninvasive electrostimulation on P6. One trial (N = 747) studied both electrostimulation and acupressure on P6. Two trials (N = 137) studied acupressure on P6 alone and P6 plus ST36. Minimal side effects were reported, including skin discomfort and irritation, transient skin rash, and electrical shock, and peripheral neuropathy in 1 patient in an electroacupuncture trial. The data were first analyzed by combining all acupuncture point stimulation modalities. Nine trials evaluated the effect of acupuncture point stimu-
ulation on acute vomiting and showed that the proportion of episodes was significantly lower in the acupuncture point stimulation group than the control (22%, 155 of 744 patients vs. 31%, 154 of 500 patients; \( P = .04 \)).\(^6,22,31–35,37–39\) The mean number of acute vomiting episodes, however, did not differ between the groups.\(^6,22,31–35,37–39\)

Those results were also reflected in both sham- and non–sham-acupuncture controlled trials.\(^22\) Among 7 trials assessing the effect of acupuncture point stimulation on acute nausea severity, no significant difference was seen between the groups (\( P = .10 \)).\(^6,22,32,33,36–38,40\) In 3 noninvasive acupuncture point stimulation trials, it had no benefit on delayed vomiting episodes (\( P = .80 \)).\(^6,22,41,42\) Results of 5 trials evaluating the effect of noninvasive acupuncture point stimulation on delayed nausea also showed no benefit (\( P = .80 \)).\(^6,22,32,37,38,40\)

The data were then analyzed according to treatment modalities. The 4 acupuncture trials (\( N = 214 \))\(^31,33,35\) showed that manual acupuncture and electroacupuncture significantly decreased the proportion of patients experiencing acute chemotherapy-induced vomiting, from 60% (71 of 119) in the control group to 37% (35 of 95) in the acupuncture group (\( P = .01 \)).\(^22\) Among these, however, the trial that used only manual acupuncture showed no difference between the groups.\(^31\) The 3 remaining trials using electroacupuncture (\( N = 139 \))\(^31,34,35\) showed that a lower proportion of patients who underwent electroacupuncture experienced acute chemotherapy-induced vomiting compared with controls; however, none of the electroacupuncture trials used an antiemetic regimen containing a 5-HT\(_3\)-receptor antagonist.\(^24\) Manual acupuncture did not significantly decrease acute chemotherapy-induced nausea either.\(^13\) None of the acupuncture trials effectively studied the effect of acupuncture on delayed CINV.\(^22\)

The 4 noninvasive electrostimulation trials (\( N = 629 \))\(^6,32,37,38\) showed that electrostimulation did not alleviate either acute or delayed CINV.\(^22\) Although the 3 trials using acupressure (\( N = 620 \))\(^32,39,40\) showed that this technique did not significantly decrease acute chemotherapy-induced vomiting (\( P = .3 \)), they did show that it significantly decreased the severity of acute chemotherapy-induced nausea (\( P = .03 \)), although none of the trials had a sham-acupressure control group.\(^22\) The effect of acupressure in reducing chemotherapy-induced nausea was further confirmed by a subsequent mini systemic review (\( N = 482 \)) comparing acupressure and usual care with usual care alone.\(^43\)

The meta-analysis by Ezzo et al.\(^22\) is the most comprehensive summary of clinical research on the role of acupuncture point stimulation in controlling CINV. Its conclusion that acupuncture point stimulation decreases the proportion of patients experiencing acute chemotherapy-induced vomiting concurred with the previous systemic review and meta-analysis.\(^44,45\) It suggested that acupressure may relieve chemotherapy-induced nausea, even though the studies were limited by lack of effective control arm to tease out placebo effect. It also suggested differences among acupuncture point stimulation modalities, showing invasive point stimulation was more effective than noninvasive point stimulation in reducing acute CINV.\(^22\) The meta-analysis by Ezzo et al.\(^22\) is cited multiple times by review articles and oncology practice guidelines.\(^30,46,47\)

The clinical relevance of this meta-analysis remains unclear because of several limitations, some noted by the authors themselves.\(^22\) First, the most robust data of this meta-analysis came from 3 electroacupuncture trials, with a combined total of only 139 patients. Such a small sample size increased the risk for sampling bias and lessened the representativeness of the data. In addition, none of the 3 electroacupuncture trials used an antiemetic regimen containing a 5-HT\(_3\)-receptor antagonist, which is part of the standard antiemetic regimen for highly emetogenic chemotherapy and subsequently caused the data to be less interpretable in current clinical practice.

Furthermore, all 11 trials predated aprepitant, making the data less clinically relevant. In addition, among the 11 trials analyzed, 9 trials stimulated P6 point alone and 2 stimulated P6 and ST36 points. In traditional Chinese medicine practice, multiple antiemetic acupuncture points, including P6, ST36, ST44, and CV12, are stimulated simultaneously. Without examining the effect of the most effective acupuncture point combination, claiming that acupuncture did not work in certain conditions is difficult. Finally, none of the studies explored the mechanism of acupuncture in reducing CINV.

A PubMed search of key words—“acupuncture,” and “chemotherapy-induced nausea and vomiting”—produced a few clinical trials that were not included
in the analysis by Ezzo et al.\(^2\) These trials investigated the additive benefit of acupuncture to 5-HT3–receptor antagonist antiemetic regimen. None of those trials, however, used the standard 3-drug antiemetic chemotherapy regimen.

Published in 2003, a Swedish clinical trial evaluated the role of acupuncture combined with ondansetron in reducing cyclophosphamide-induced nausea and vomiting in patients with rheumatic diseases.\(^4\) It was a small study with 39 patients treated with acupuncture P6 or in the ear unilaterally or bilaterally. Using the patients as their own controls, the investigators showed that the combined acupuncture/ondansetron treatment was superior to ondansetron treatment alone in reducing CINV (nausea: \(P < .0001\); vomiting: \(P < .0035\)).\(^4\) This study, however, was limited by its small sample size, complicated, difficult-to-follow study design, and, especially, the lack of effective blinding device and control group.

In 2005, Roscoe et al.\(^4\) published a 3-arm clinical trial examining the effect of acustimulation wrist bands in reducing CINV in patients with breast cancer. It was a large sample-size, well-designed study with 96 patients experiencing chemotherapy-induced nausea randomized into active acustimulation, sham acustimulation, or no stimulation arm. No difference was seen among the 3 arms in acute nausea, delayed nausea, vomiting, quality of life, or antiemetic medication use. The selection of the sham point for acustimulation, which is an active acupuncture point by itself—Triple Heater 5 point—may be used to explain the lack of difference between the real versus sham acustimulation. However, the lack of difference between the no-stimulation and the other 2 arms is difficult to explain. The question of the efficacy of self-administered acustimulation in controlling CINV is subsequently raised.

In 2007, an acupressure study of 100 oncology patients undergoing chemotherapy and experiencing breakthrough CINV despite antidopaminergics and antiemetic regimens containing a 5-HT3–receptor antagonist showed that 68% patients experienced relief with P6 acupressure treatment.\(^5\)

In 2008, Guttschling et al.\(^6\) published the final result of a randomized multicenter crossover study of 23 pediatric oncology patients treated with highly emetogenic chemotherapy and undergoing a concurrent 5-HT\(_3\)–receptor antagonist antiemetic regimen. It showed a significantly lower need for rescue antiemetic medication (\(P = .001\)) and fewer episodes of acute chemotherapy-induced vomiting (\(P = .01\)) in the acupuncture treatment group than the no acupuncture control group.\(^6\) This trial is unique because it allowed experienced acupuncturists to decide which acupuncture points to use and thus provided individualized acupuncture treatment to the patients; the most commonly used points were PC6, ST36, CV12, and LI4. However, it is limited by its small sample size, crossover design that could introduce carry-over effect, and lack of sham acupuncture control arm.

Although all of these trials investigated the additional benefit of acupuncture/acupressure to 5-HT3–receptor antagonist, all of them predated aprepitant, and none used a concurrent 3-drug antiemetic regimen. It is encouraging to note that the more modern acupuncture studies have begun to use more acupuncture points to control CINV. Those studies, however, did not have effective sham-acupuncture control arms to tease out placebo effect. In addition, none of the studies explored the mechanism of acupuncture in controlling CINV.

**Conclusions**

Current acupuncture research on CINV is limited by small sample size and outdated concurrent antiemetic pharmacologic therapy. However, studies suggest a role of acupuncture in controlling CINV even though its implication in the current clinical practice remains unclear. Further acupuncture research should consider using additional antiemetic acupuncture points, with bigger sample sizes, an effective sham acupuncture control arm, and as adjunct to the standard 3-drug antiemetic regimen. Further acupuncture research should also explore the mechanism of acupuncture.

**References**


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