Background: German anesthesiologists have long used transcutaneous electrical stimulation of an acupuncture point near the tragus to reduce anesthetic requirement in unblinded and uncontrolled trials. This is known as auricular electrically stimulated analgesia. The authors therefore tested the hypothesis that auricular electrically stimulated analgesia reduces anesthetic requirement.

Methods: In a randomized, double-blind, crossover trial, volunteers were anesthetized twice with desflurane. Electrical stimulation of an auricular acupuncture point in the vicinity of the tragus was used on 1 randomly assigned day, and no electrical stimulation of the same point was used on the other study day. Treatment consisted of bilateral electrical stimulation of the lateralization control point, 3 cm anterior to the tragus. The 10-mA current was set to 299 Hz on the dominant side of the face and to 149 Hz on the contralateral side. Anesthetic requirement was determined by the average desflurane concentration required to prevent purposeful movement of the extremities in response to noxious electrical stimulation.

Results: Ten men and 10 women completed the protocol. Electrical stimulation of the lateralization control point reduced anesthetic requirement by 11 ± 7% (P < 0.001), with the reduction being similar in women and men. Women required more desflurane to prevent movement on the control day than the men (5.5 ± 1.0 vs. 4.6 ± 0.6 vol%; P = 0.028).

Conclusion: This double-blinded trial with an objective outcome demonstrates that electrical stimulation of the lateralization control point significantly reduces anesthetic requirement.

ACUPUNCTURE is based on patterns of energy flow through the body, with disruptions of this flow being thought to cause disease. The scientific basis for acupuncture remains unclear because the traditional system of acupuncture points does not correspond to western concepts of anatomy or neurology. Nonetheless, it has been shown that acupuncture releases neurochemical substrates such as endorphins, serotonin, and norepinephrine. Acupuncture has been used extensively since being developed in China 2,500 yr ago, and it remains widely used throughout Asia.

Despite a large literature, acupuncture has not received the kind of stringent evaluation that would now be required for new drugs or medical devices. For example, a recent National Institutes of Health consensus statement noted the following:

According to contemporary research standards, there is a paucity of high-quality research assessing efficacy of acupuncture compared with placebo or sham acupuncture. The vast majority of papers studying acupuncture in the biomedical literature consist of case reports, case series, or intervention studies with designs inadequate to assess efficacy.

Lack of adequate validation has not stopped acupuncture from becoming popular in the United States. Millions of Americans have been treated with acupuncture for a variety of pain states and other conditions. However, it is disconcerting that this increasingly popular pain treatment has yet to be adequately evaluated—especially given the substantial potential for bias and placebo effect in unblinded or only partially blinded pain studies.

Difficulty with blinding has proven one of the major impediments to adequate validation studies. During general anesthesia is one time when it is possible to completely double-blind acupuncture treatments. To the extent that acupuncture provides analgesia, it might be expected to reduce the need for conventional anesthetic drugs. German anesthesiologists have used electrical stimulation of acupuncture points to reduce the need for anesthetics. They initially used needle acupuncture and subsequently conventional adhesive electrodes. Each reported more than a 70% reduction in anesthetic requirement; however, the studies were neither double blinded nor placebo controlled.

In this double-blind, placebo-controlled study, we therefore tested the hypothesis that transcutaneous electrical stimulation of one auricular acupuncture point (bilateral electrical stimulation of the lateralization control point, an area in the vicinity of the ear tragus) reduces anesthetic requirement after acute noxious stimulation.
Methods

After obtaining approval from the Committee on Human Research at the University of California–San Francisco and written informed consent, we studied 24 healthy volunteers of either gender, aged between 18 and 40 yr. None had a history of drug addiction, and none took any drugs other than oral contraceptives. Twenty of the volunteers completed the protocol. Menstrual cycle was not controlled because cycle status has little or no influence on perception of experimental pain.8

Protocol

Volunteers fasted and refrained from smoking for at least 8 h before arriving at the laboratory. No premedication was given. The volunteers who completed the trial participated on 2 study days, separated at least by at least 48 h (8 ± 5 days, mean ± SD). Each set of studies began at the same time of day because circadian rhythms can influence anesthetic requirement.9

The volunteers rested supine on a standard operating room table set in a chaise-longue position. A catheter was inserted in a left forearm vein for fluid and drug administration. On each study day, anesthesia was induced with approximately 4 mg/kg intravenous propofol. After loss of the eyelash reflex, a pharyngeal airway (GO2; Augustine Medical, Inc., Eden Prairie, MN) was inserted. We used a pharyngeal airway rather than tracheal intubation to minimize airway stimulation. Ventilation was assisted until spontaneous breathing was re-established. Anesthesia was initially maintained with desflurane 5.5% end-tidal partial pressure in 30% oxygen and 70% nitrogen. Hypothermia reduces anesthetic requirement approximately 5% per degree centigrade.10 We thus used forced-air heating (Bair Hugger; Augustine Medical, Inc.) to maintain core temperature near 36°C.

After induction of anesthesia on the initial study day, volunteers were randomly assigned to transcutaneous electrical stimulation of an auricular acupuncture point (auricular electrically stimulated analgesia [AESA]) or no treatment (control). Randomization was based on computer-generated codes that were maintained in sequentially numbered opaque envelopes. We used a double-blinded crossover study design: each volunteer was thus given the alternative treatment (AESA or control) on the second study day.

We bilaterally stimulated an auricular acupuncture point, the lateralization control point, 3 cm anterior to the top of the tragus (fig. 1).7 Transcutaneous electrical stimulation was chosen because it is easier to use and blind than conventional dry needles. Pediatric-sized, electrocardiogram electrodes were positioned just above the lateralization control point, with the ground electrode positioned just below it. The AESA electrodes were connected to a TNS-SM 2L stimulator (Schwa-medico, Pierenkemper, Germany). This battery-powered stimulator is approximately 11 × 6.5 × 3.5 cm. As recommended by Heinze et al.,11 the stimulating frequency was set to 299 Hz on the dominant side of the face and to 149 Hz on the contralateral side. Both frequencies are reportedly effective at the lateralization control point. The current was set to 10 mA; we used a positive rectangle waveform, with an impulse duration of 0.2 ms.

The cutaneous electrodes were positioned on each study day but they were stimulated only on the AESA day. The stimulator was activated or not activated by an investigator who was not otherwise involved in the study, and locked into a sturdy metal box throughout the study to blind the remaining investigators. The electrodes were connected on each study day by the independent investigator after insertion of the airway so the volunteers would not sense the “tingling” sensation produced by the electric current. Occasionally, a 10-mA current applied to the lateralization control point causes slight constriction of the orbicularis oculi. The entire upper face was therefore covered with a bulky gauze bandage that concealed any muscle twitching. The gauze was securely taped into position to assure that it
remained in place throughout the entire anesthetic period. Electrical stimulation began soon after induction and continued throughout anesthesia.

Anesthetic requirement was defined by the average partial pressure of desflurane required to prevent movement in response to noxious electrical stimulation. Electrical stimulation was given by two 25-gauge needles that were inserted intradermally into the lower portion of each anterior thigh. A bilateral 65–70 mA, 100-Hz tetanic electrical current, maintained for 10 s, provided the noxious stimulus. A tetanic stimulus even 20% of this intensity is unbearable to unanesthetized subjects. To prevent desensitization of nerves at the needle insertion site, the electrodes were moved cranially by 1 cm after each stimulation.

We first evaluated movement after the end-tidal desflurane concentration was constant at 5.5 vol% for 15 min. If the volunteer moved in response to noxious electrical stimulation, the desflurane concentration was subsequently increased by 0.5 vol%. In contrast, the desflurane concentration was reduced by 0.5 vol% when the volunteer did not move. A positive response to noxious electrical stimulation was defined by purposeful movement of one or more extremities. Grimacing and head movement were not considered purposeful responses. The new end-tidal desflurane partial pressure was maintained for 15 min to allow alveolar-to-brain equilibration, and the process was repeated. We continued this up-and-down sequence until the volunteer "crossed over" from movement to nonmovement four times. This paradigm is referred to as the Dixon up-and-down method,12 and it is the standard technique for evaluating anesthetic potency.13 Anesthesia was then discontinued, and the study day was ended after a suitable period of supervised recovery.

**Measurements**

We recorded morphometric and demographic characteristics of the volunteers. End-tidal desflurane volume-percent and carbon dioxide were measured using an Ohmeda Rascal monitor (Ohmeda Inc, Salt Lake City, UT) that was calibrated daily. The accuracy of the Rascal monitor is 0.1% desflurane. Steady state end-tidal concentrations of volatile anesthetics and carbon dioxide are virtually identical to alveolar and brain concentrations.14 Heart rate and blood pressure were determined oscillometrically (Modulus CD; Ohmeda) at 5-min intervals and before each tetanic stimulation. A pulse oximeter continuously determined arterial oxygen saturation. Core temperature was measured from the tympanic membrane using Mon-α-Therm® thermocouples (Mallinckrodt Anesthesiology Products, Inc. St. Louis, MO).

**Data Analysis**

A sample-size estimate based on a preliminary study suggested that 20 subjects would provide 90% power to detect a difference in anesthetic requirements between AESA and control of approximately 1.5% desflurane (30%) with a SD of 2%.

Hemodynamic responses, core temperature, and end-tidal carbon dioxide tension were first averaged over each study day for each volunteer, and then averaged among the volunteers given each treatment. Logistic regression was used to determine the end-tidal desflurane that produced a 50% likelihood of movement in response to noxious stimulation. Briefly, all desflurane concentrations with and without movement were entered into a logistic regression. A typical logistic regression is shown in figure 2. The desflurane concentrations with and without AESA that were associated with a 50% chance of movement were compared with a two-tailed paired t test.

Values in men and women were compared with two-tailed unpaired t tests. Results are presented as mean ± SD; P < 0.05 was considered statistically significant.

**Results**

Fourteen women and 10 men enrolled in the trial. Five men were initially assigned to AESA and five to control; all of the men completed both study days. Six women were initially assigned to AESA; two withdrew from the study after the first day because of severe postoperative
noura and vomiting. Eight women were initially assigned to a control day; two withdrew from the study after the first day because of severe postoperative nausea and vomiting. Ten men and 10 women thus completed both study days. Data analysis was restricted to these 20 volunteers.

Among the volunteers completing the trial, three men (two after AESA—general anesthesia and two after control—general anesthesia) and four women (two after AESA—general anesthesia and three after control—general anesthesia) developed postanesthetic nausea or vomiting. Total duration of the study was 171 ± 49 min on the AESA day and 169 ± 40 min on the control day (P = 0.8). Potential confounding factors were similar on the AESA and control study days (table 1). As might be expected, the women were significantly shorter and lighter than the male volunteers. The women also had lower mean arterial pressures and higher heart rates, and a slightly lower end-tidal carbon dioxide pressure (table 2).

Table 1. Potential Confounding Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>Control</th>
<th>AESA</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction propofol (mg/kg)</td>
<td>4.3 ± 0.6</td>
<td>4.4 ± 0.8</td>
<td>0.57</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>66 ± 10</td>
<td>66 ± 7</td>
<td>0.73</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64 ± 10</td>
<td>69 ± 12</td>
<td>0.18</td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>36.4 ± 0.3</td>
<td>36.4 ± 0.3</td>
<td>0.63</td>
</tr>
<tr>
<td>End-tidal Pco₂ (mmHg)</td>
<td>45 ± 3</td>
<td>46 ± 3</td>
<td>0.32</td>
</tr>
<tr>
<td>AESA Stimulus left side (mA)</td>
<td>9.9 ± 0.3</td>
<td>9.9 ± 0.2</td>
<td>0.88</td>
</tr>
<tr>
<td>AESA Stimulus right side (mA)</td>
<td>10.0 ± 0.1</td>
<td>9.9 ± 0.2</td>
<td>0.36</td>
</tr>
<tr>
<td>Time to first cross-over (min)</td>
<td>95 ± 20</td>
<td>100 ± 36</td>
<td>0.57</td>
</tr>
</tbody>
</table>

Ten male and ten female volunteers each participated on one control and one AESA day; each value is thus the mean (± SD) of twenty studies. Crossover was defined by the transition from movement to no movement in response to noxious electrical stimulation. Values were compared with 2-tailed, paired t tests. There were no statistically-significant differences between the treatment days. AESA = auricular electrically stimulated analgesia.

Transcutaneous electrical stimulation applied to the lateralization control point reduced anesthetic requirement 11% (P < 0.001; fig. 3). The reduction was similar in women (13%; 95% confidence interval, 9–17%) and men (9%; 95% confidence interval, 6–12%) (P = 0.20). The women required a greater desflurane concentration to prevent movement on the control day than the men (5.5 ± 1.0 vs. 4.6 ± 0.6 vol%; P = 0.028; table 3 and fig. 3). When data from the four women who withdrew after the first study day were included in an unpaired analysis, differences between men and women and between AESA and control treatments remained statistically significant.

Discussion

Successful anesthetics provide analgesia, prevent awareness and recall, and forestall patient movement. These components can be provided by a single drug such as a volatile anesthetic or can be provided individually by combining drugs such as opioids, amnestics, and muscle relaxants. Potency of inhaled anesthetics is con-

Table 2. Differences between Men and Women on the Control Day

<table>
<thead>
<tr>
<th>Metric</th>
<th>Men (n = 10)</th>
<th>Women (n = 10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (cm)</td>
<td>172 ± 6</td>
<td>165 ± 4</td>
<td>0.004</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>73 ± 10</td>
<td>59 ± 8</td>
<td>0.003</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>28 ± 5</td>
<td>26 ± 6</td>
<td>0.416</td>
</tr>
<tr>
<td>Induction propofol (mg/Kg)</td>
<td>4.2 ± 0.4</td>
<td>4.3 ± 0.7</td>
<td>0.579</td>
</tr>
<tr>
<td>Mean arterial pressure (mmHg)</td>
<td>68 ± 7</td>
<td>63 ± 5</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>64 ± 10</td>
<td>69 ± 8</td>
<td>0.030</td>
</tr>
<tr>
<td>Core temperature (°C)</td>
<td>36.3 ± 0.3</td>
<td>36.5 ± 0.2</td>
<td>0.144</td>
</tr>
<tr>
<td>End-tidal Pco₂ (mmHg)</td>
<td>47 ± 3</td>
<td>44 ± 2</td>
<td>0.033</td>
</tr>
<tr>
<td>AESA Stimulus left side (mA)</td>
<td>10.0 ± 0.2</td>
<td>9.9 ± 0.3</td>
<td>0.610</td>
</tr>
<tr>
<td>AESA Stimulus right side (mA)</td>
<td>10.0 ± 0.2</td>
<td>10.0 ± 0.0</td>
<td>0.357</td>
</tr>
<tr>
<td>Time to first cross-over (min)</td>
<td>107 ± 43</td>
<td>94 ± 29</td>
<td>0.041</td>
</tr>
</tbody>
</table>

Crossover was defined by the transition from movement to no movement in response to noxious electrical stimulation. Values are presented as means ± SDs. Values were compared with 2-tailed, unpaired t tests. AESA = auricular electrically stimulated analgesia.

Table 3. Threshold for Movement

<table>
<thead>
<tr>
<th>Desflurane (Volume Percent)</th>
<th>Control</th>
<th>AESA</th>
<th>Difference (Percent)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men (n = 10)</td>
<td>4.6 ± 0.6*</td>
<td>4.2 ± 0.6</td>
<td>9 ± 7</td>
<td>0.001</td>
</tr>
<tr>
<td>Women (n = 10)</td>
<td>5.5 ± 1.0</td>
<td>4.7 ± 0.6</td>
<td>13 ± 7</td>
<td>0.001</td>
</tr>
<tr>
<td>Men and Women</td>
<td>4.9 ± 0.7</td>
<td>4.4 ± 0.6</td>
<td>11 ± 7</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Desflurane concentrations and differences between control and AESA are presented as mean ± SDs. Asterisks (*) indicate statistically significant differences between men and women. AESA = auricular electrically stimulated analgesia.
ventionally expressed in terms of minimum alveolar concentration, the partial pressure at which 50% of patients move in response to a surgical skin incision. The potency of intravenous anesthetics can be expressed in terms of the analogous drug concentration in the plasma at which 50% of the subjects move. Movement in both cases is an unconscious reflex apparently mediated by the spinal cord. Furthermore, the anesthetic partial pressure preventing recall is between a third and a half of that preventing movement. Patients participating in studies of anesthetic depth are therefore not conscious of pain, nor do they remember the incision.

The difficulty with using skin incision to determine anesthetic potency is that studies are restricted to surgical patients, each of whom contributes only a single “move” or “no move” data point. A further difficulty is that the amount of pain experienced by surgical patients depends on numerous factors in addition to the magnitude of surgery per se. For example, gender, ethnicity, psychological state, and resting blood pressure all influence pain perception and analgesic requirement. We and other investigators have therefore used transcutaneous electrical current to provide an intense painful stimulus. In this modification of the classic technique, anesthetic requirement is determined by the drug partial pressure or plasma concentration required to prevent movement in response to noxious electrical stimulation.

The major advantage of using noxious electrical stimulation instead of surgical skin incision is that it permits the use of a crossover design that minimizes the effects of extraneous factors. Anesthetic requirement determined with electrical stimulation is invariably less than that determined from skin incision. Electrical stimulation is nonetheless a sensitive and well-accepted method for evaluating factors that influence anesthetic requirement.

Acupuncture has been reported to be effective in numerous unblinded and sham-controlled trials whereas other investigators reported no benefit. However, it is rarely possible to blind patients to the use of acupuncture needles. Consequently, control patients are often given sham treatments, with the needles positioned at sites that are believed to be ineffective. An obvious problem with this approach is that the acupuncture practitioner might easily convey a bias to the patient. However, the National Institutes of Health consensus statement identified additional concerns:

- Particularly in the studies on pain, sham acupuncture often seems to have either intermediate effects between the placebo and “real” acupuncture points or effects similar to those of the “real” acupuncture points. Placement of a needle in any position elicits a biologic response that complicates the interpretation of studies involving sham acupuncture. Thus, there is substantial controversy over the use of sham acupuncture in control groups.

- Lewith and Machin described the extensive limitations of using sham treatments as controls. Their analysis makes it obvious that sham treatments are a poor substitute for truly double-blinded placebo-controlled studies. Other investigators have concluded the same thing.

The current study is a double-blinded, placebo-controlled trial demonstrating that transcutaneous electrical stimulation of an auricular acupuncture point reduces requirement for a volatile anesthetic. As a further precaution against bias, we evaluated an objective response: purposeful movement of the extremities. We found that acupuncture reduced desflurane requirement by 11% (P < 0.001), thus confirming our first hypothesis. Our results are consistent with previous unblinded studies in animals.

As in previous acupuncture studies, we found that approximately 10% of the subjects were nonresponders. However, our analysis includes all volunteers that completed both study days and thus fairly represents the reduction in anesthetic requirement that might be expected in the general population. Reducing anesthetic requirement benefits surgical patients because anesthetic-induced toxicity is dose-dependent; furthermore, recovery duration is largely a function of anesthetic dose. The observed reduction in anesthetic requirement was highly statistically significant but of relatively small magnitude. These results nonetheless provide an important proof of principle and suggest that other types of acupuncture may provide clinically important benefit.

A number of chronic conditions are known to cause more pain in women than men. However, these differences are difficult to evaluate because disease severity, or at least activation of pain pathways, may be enhanced in women. Sex differences in the response to presumably uniform experimental pain have also been reported by some investigators whereas others report little or no difference. A limitation of all of these studies is that pain is inherently subjective, and the response to pain can be markedly significantly influenced by social factors.

An ancillary finding in our study was that women required 20% more desflurane to prevent movement on the control day than the men (5.5 ± 1.0 vs. 4.6 ± 0.6 vol%; P = 0.028). Because movement in response to noxious electrical stimulation is a nonvolitional, unconscious response, we can assume that the observed gender difference did not result from social conditioning. That indicates that there is a fundamental difference in the response of women and men to noxious stimuli. This is consistent with previous work but is the first objective evidence that comparable noxious stimuli provoke greater responses in women than men and is consistent with the observation that female rats are more sensitive than male rats to experimental neuropathic pain.
We stimulated the lateralization control point because it has been used intraoperatively and is believed to produce generalized (as opposed to site-specific) analgesia. Electrical stimulation of this auricular acupuncture point allowed us to fully double-blind the protocol, whereas adequate blinding would be difficult with conventional needles. An additional advantage of transcutaneous electrical stimulation of an auricular acupuncture point is that the technique is simple, precluding the need for formal training in needle acupuncture. Specifically, there is no need for training in needle insertion technique, depth, and direction of puncture, or the need for manual stimulation as is used in traditional Chinese medicine. Furthermore, the face is a convenient location for perioperative acupuncture because the head is usually readily accessible to anesthesiologists.

The electroacupuncture stimulator we used provided 299 and 149 Hz, frequencies that are not found so many acupuncture studies. We stimulated the lateralization control point between electroacupuncture and transcutaneous electrical nerve stimulation unit that typically stimulates at a frequency between 2 and 100 Hz. Generally, 2- or 100-Hz transcutaneous electrical nerve stimulation is used to treat pain, although a mixture of 2 and 100 Hz has also been advocated. However, the critical difference between electroacupuncture and transcutaneous electrical nerve stimulation is that we stimulated at a site far remote from the pain site.

Four women and no men withdrew from the study. However, the results remained highly statistically significant when available data from all 14 women were included in the analysis. It thus seems unlikely that our results are biased by the women who declined to finish the study. A more important distinction is between volunteers and surgical patients. The actual reduction in anesthetic requirement may differ in surgical patients or volunteers and surgical patients. The actual reduction in anesthetic requirement may differ in surgical patients or volunteers and surgical patients. The actual reduction in anesthetic requirement may differ in surgical patients or volunteers and surgical patients. The actual reduction in anesthetic requirement may differ in surgical patients or volunteers and surgical patients. The actual reduction in anesthetic requirement may differ in surgical patients or volunteers and surgical patients.

In summary, our results indicate that transcutaneous electrical stimulation of the lateralization control point reduces the desflurane concentration required to prevent movement in response to noxious stimulation by 11%. Our randomized double-blind study design allowed a truly placebo-controlled comparison of the treatment effect, thus avoiding the types of bias that confound so many acupuncture studies.

The authors greatly appreciate the assistance of Angela Rajek, M.D. (Department of Cardiovascular and Thoracic Anesthesia, University of Vienna, Vienna, Austria).

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