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Effect of the Frequency of Transcutaneous Electrical Nerve Stimulation on the Postoperative Opioid Analgesic Requirement and Recovery Profile

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Background: **Transcutaneous electrical nerve stimulation (TENS) at either an acupoint or dermatome corresponding to the surgical incision produces comparable decreases in postoperative opioid requirements and opioid-related side effects. However, the effect of the frequency of the electrical stimulus on the postoperative analgesic response to TENS therapy has not been studied.**

Methods: **One hundred women undergoing major gynecological procedures with a standardized general anesthetic technique were enrolled in the study. Patients were randomly assigned to four groups: group I, patient-controlled analgesia (PCA) plus sham TENS (no stimulation); group II, PCA plus low-frequency (2-Hz) TENS; group III, PCA plus high-frequency (100-Hz) TENS; group IV, PCA plus mixed-frequency (2- and 100-Hz) TENS. The PCA device was programmed to deliver 2–3 mg intravenous boluses of morphine with a lockout interval of 10 min. The TENS device was used every 2 h during the day. Standard 100-mm visual analog scales were used to assess pain, sedation, fatigue, and nausea at specific intervals after surgery.**

Results: **Mixed frequency (2 and 100 Hz) of stimulation decreased morphine requirements by 53% compared with the sham group; low (2-Hz) and high (100-Hz) frequencies produced 32% and 35% decreases, respectively. All three "active" TENS groups reduced the duration of PCA therapy, as well as the incidence of nausea, dizziness, and itching.**

Conclusions: **TENS decreased postoperative opioid analgesic requirements and opioid-related side effects when utilized as an adjunct to PCA after lower abdominal surgery. Use of TENS at mixed (2- and 100-Hz) frequencies of stimulation produced a slightly greater opioid-sparing effect than either low (2-Hz) or high (100 Hz) frequencies alone. (Key words: Acute pain; electroanalgesia.)**

TRANSCUTANEOUS electrical nerve stimulation (TENS) at both Chinese acupoints and dermatomal levels corresponding to the surgical incision have been reported to significantly decrease postoperative opioid requirements and the incidence of opioid-related side effects.[1–4] The effectiveness of TENS in reducing the need for opioid analgesics has recently been shown to be influenced by both the location and intensity of the electrical stimulus.[1,2] However, controversy exists regarding the optimal frequency of electrical stimulation with TENS.[5–8]

Walsh *et al.*[6] suggested that a low frequency (4 Hz) of stimulation had a greater analgesic effect than high-frequency (100-Hz) stimulation using an experimental pain model. In contrast, Johnson *et al.*[7] reported that the use of high-frequency stimulation produced greater analgesic effects. Hansson and Ekblom[8] reported comparable analgesic effects at both low and high frequencies of stimulation; however, the patients "preferred" high-frequency stimulation. It has also been reported that low-frequency stimulation requires a higher intensity to produce pain relief equivalent to high-frequency stimulation.[9] The effect of alternating low- and high-frequency ("mixed") stimulation on the postoperative analgesic requirement has not been previously studied in man.

This prospective, randomized, sham-controlled study was designed to test the hypothesis that the frequency of the electrical stimulation influences the opioid-sparing effects of TENS therapy. The effects of low, high, and mixed frequencies of electrical stimulation on the postoperative requirement for morphine with patient-controlled analgesia (PCA), the incidence of opioid-related

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side effects, and the recovery profile after lower abdominal surgery were assessed.

Methods

After obtaining written, informed consent, 100 patients with American Society of Anesthesiologists physical status I or II scheduled to undergo elective lower abdominal gynecologic surgery (*e.g.*, hysterectomy or myomectomy procedures) were enrolled in this institutional review board–approved sham-controlled study. The patients were randomly assigned to one of four postoperative analgesic treatment groups according to a computer-generated randomization sequence (n = 25 each): group I (control), PCA plus sham TENS (there was no electrical stimulation, but the functional indicator lights were flashing normally); group II, PCA plus low-frequency (2-Hz) TENS; group III, PCA plus high-frequency (100-Hz) TENS; and group IV, PCA plus mixed-frequency (alternating at 2 and 100 Hz every 3 s) TENS. The operational aspects of the PCA device (LIFECARE PCA plus II infuser; Abbott Laboratories, North Chicago, IL) and the investigational TENS stimulator (Hans LY267, Healthtronics, Singapore, Singapore) were explained to each patient during the preoperative visit and subsequently reviewed with the patient prior to initiating PCA therapy in the postanesthesia care unit. Patients with a history of narcotic (opioid) analgesic abuse, prior use of a TENS device, or sensitivity to opioid-related side effects, as well as those with clinically significant cardiovascular, pulmonary, renal, hepatic, and neurologic diseases, were excluded from participating in this study.

All patients received midazolam, 1–2 mg intravenously, for premedication immediately prior to entering the operating room. Anesthesia was induced with thiopental, 4 mg/kg intravenously, and fentanyl, 1–2 μg/kg intravenously, and maintained with desflurane 3–6% and nitrous oxide 60% in oxygen. Tracheal intubation was facilitated with rocuronium, 0.6 mg/kg intravenously, and residual neuromuscular blockade was reversed with a combination of neostigmine, 0.050–0.075 mg/kg, and glycopyrrolate, 0.005–0.010 mg/kg intravenously, at the end of the operation. Morphine, 75 μg/kg intravenously, was administered before the end of surgery. No additional opioid analgesic medications were administered during the intraoperative period.

On a patient's arrival in the postanesthesia care unit, the PCA device was connected to the patient's intravenous line and programmed to deliver 2- to 3-ml bolus doses of morphine (2–3 mg) "on demand," with a minimal lockout interval of 10 min and a maximum 4-h dose of 20 mg according to a standardized hospital protocol. PCA therapy was initiated in the postanesthesia care unit when the patient was sufficiently alert to understand and operate the PCA device. If the patient required pain medication prior to initiating PCA therapy, incremental doses of morphine, 1.5–3.0 mg intravenously, were administered by the postanesthesia care unit nursing staff. The postoperative PCA analgesic therapy was supplemented with TENS therapy, which was started when the patient arrived in the postanesthesia care unit and continued for 30 min at intervals of 2 h or longer while the patient was awake, as well as at bedtime and when the patient awakened from sleep. The TENS device automatically shuts off at the end of each 30-min treatment interval. Two sets of 2×2-in (26-cm^2) stimulating pads (Soft Touch 7000 electrodes, Empi, St. Paul, MN) were positioned on either side of the surgical incision at adjacent dermatomal levels as illustrated in figure 1. The electrodes were connected to the TENS device and stimulated in a synchronized fashion with a bidirectional electrical current wave and a pulse width that changed automatically within a range of 0.2–0.6 ms. The intensity of the electrical stimulation was set at 0 mA for group I and at 9–15 mA (*i.e.*, the highest tolerated amplitude of electrical stimulation) in groups II, III, and IV. Patients in group I were told that they may not be able to feel the electrical stimulation; however, the "in use" light on the TENS device was flashing in the usual manner when it was activated. None of the patients were aware of the frequency of electrical stimulation being applied during the study period. The ward nurse recorded the number

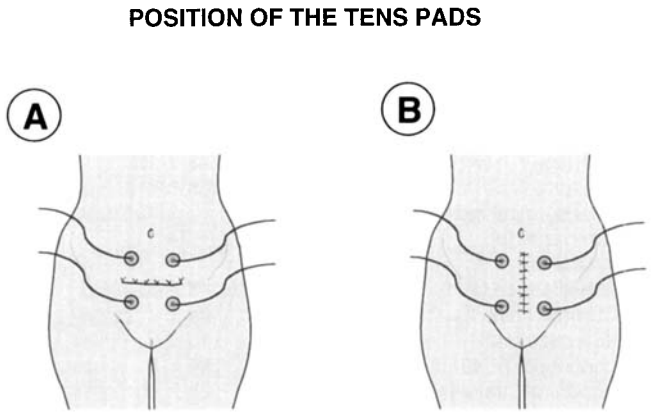

Fig. 1. Four cutaneous electrode pads were positioned at the dermatomal levels corresponding to the horizontal (*A*) or vertical (*B*) skin incision.

Table 1. Demographic, Clinical, and Recovery Characteristics for the Four Treatment Groups

	Control (sham TENS)	2 Hz (low TENS)	100 Hz (high TENS)	2/100 Hz (mixed TENS)
Number (n)	25	25	25	25
Age (yr)	43 ± 9	43 ± 11	44 ± 11	45 ± 10
Weight (kg)	73 ± 12	69 ± 14	68 ± 16	71 ± 10
Height (cm)	168 ± 6	169 ± 7	167 ± 5	168 ± 6
Type of surgical incision				
Transverse (n)	24	23	25	23
Vertical (n)	1	2	0	2
Anesthesia time (min)	143 ± 56	146 ± 45	152 ± 35	147 ± 43
PACU time (min)	64 ± 7	66 ± 10	68 ± 12	65 ± 9
TENS usage (n)	15 ± 2	14 ± 2	14 ± 3	15 ± 3
Discontinued TENS (h)	34 ± 8	36 ± 8	35 ± 10	38 ± 11
Resume oral intake (h)	25 ± 6	23 ± 4	25 ± 5	22 ± 4
Hospital discharge (days)	4 ± 1	3 ± 1	4 ± 2	4 ± 1

Values are mean ± SD or number (n).

TENS = transcutaneous electrical nerve stimulation; Mixed TENS = alternating frequency at 2 and 100 (2/100) Hz of TENS; PACU = postanesthesia care unit.

of times the patients activated the TENS device and recorded any untoward side effects.

The PCA therapy was discontinued when the patient no longer required parenteral analgesic therapy. The TENS therapy was discontinued when the patient was able to control his or her pain with oral analgesic medication (*e.g.*, acetaminophen with codeine). Supplemental doses of morphine (3–5 mg) were administered intramuscularly if the patient was unable to achieve adequate analgesia with the PCA device. Opioid-related side effects (*e.g.*, postoperative nausea, vomiting, and pruritis) were treated according to a standardized hospital protocol if the patient complained of persistent symptoms on successive nursing visits.

The number of PCA demands (*i.e.*, times the button was pressed) and delivered bolus doses during each subsequent 8-h interval were recorded by a "blind" observer (who was not aware of the type of TENS therapy being administered). In addition to assessing the postoperative analgesic requirements, opioid-related side effects and the requirements for supplemental medications (*e.g.*, antiemetics, antipruritics, and analgesics) were recorded during the 48-h postoperative observation period. Standard 100-mm visual analog scales were used to assess the patient's levels of sedation (from 0, awake and alert, to 100, almost asleep), fatigue (from 0, well rested, to 100, exhausted), discomfort (from 0, extremely comfortable, to 100, extremely uncomfortable), pain (from 0, no pain, to 100, worst pain imaginable), and nausea (from 0, no nausea, to 100, severe nausea).[1,2,7] *Pain* was used to refer to the painful sensation in the area of the surgical incision, and *discomfort* to unpleasant "whole body" feelings. The visual analog scale assessments were performed before administration of the midazolam premedication (baseline), and at 24 and 48 h after the operation. A pain-assessment questionnaire was also completed by the patients at the time of discharge.

An *a priori* power analysis was performed to determine the number of patients per group sufficient to detect a decrease of 30% or more in the PCA opioid analgesic requirements during the first 24 h after surgery, based on the results of the preliminary studies.[1,2] The patient's age, weight and height, duration of surgery, PCA demands and delivered doses, postoperative analgesic usage, scores, and recovery times were analyzed using one-way analysis of variance (ANOVA). A Bonferroni correction was performed for multiple comparisons. The incidence of side effects and the requirements for supplemental medications were compared among the four groups using chi-square analysis or the Fisher exact test, as appropriate. Data are presented as mean values ± SD, with P values < 0.05 considered statistically significant.

Results

The four treatment groups were comparable with respect to demographic, clinical, and recovery characteristics (table 1). The number of PCA demands and delivered doses of morphine during the first 24 h after the operation were significantly decreased in groups II, III, and IV compared with group I (table 2). Although the duration of PCA pump use was significantly shorter in groups II, III, and IV compared with group I, this differ-

Table 2. Postoperative Analgesic Requirements in the Four Treatment Groups

	Control (sham TENS)	2Hz (low TENS)	100Hz (high TENS)	2/100Hz (mixed TENS)
PCA demands in the first 24 h (n)				
0–8 h	17 ± 11	9 ± 6*	10 ± 8*	9 ± 6*
8–16 h	18 ± 13	11 ± 8*	9 ± 6*	8 ± 5*
16–24 h	15 ± 11	9 ± 8*	8 ± 6*	6 ± 4*
Total in 24 h	50 ± 28	29 ± 16*	27 ± 13*	23 ± 10*
PCA doses in the first 24 h (n)				
0–8 h	8 ± 4	6 ± 4*	5 ± 3*	5 ± 2*
8–16 h	7 ± 3	6 ± 3*	5 ± 2*	3 ± 1*†‡
16–24 h	6 ± 3	4 ± 2*	4 ± 2*	3 ± 1*
Total in 24 h	20 ± 7	15 ± 6*	14 ± 5*	10 ± 3*†‡
PCA morphine dosage (mg)				
0–8 h	23 ± 11	17 ± 10*	16 ± 8*	14 ± 6*
8–16 h	21 ± 8	17 ± 9*	15 ± 5*	9 ± 3*†‡
16–24 h	17 ± 9	12 ± 6*	13 ± 6*	8 ± 4*
Total in 24 h	61 ± 20	45 ± 17*	44 ± 14*	31 ± 8*†‡
After 24 h	11 ± 10	3 ± 6*	4 ± 5*	2 ± 4*
Total	72 ± 25	49 ± 18*	47 ± 15*	34 ± 11*†‡
Discontinued PCA therapy (h)	35 ± 8	26 ± 4*	27 ± 5*	24 ± 4*
Supplemental (rescue) opioid doses				
In the first 24 h (n)	5	4	5	3
After 24 h (n)	4	4	3	4
Oral analgesics (n)	6 ± 4	5 ± 2	5 ± 3	4 ± 2
Acetaminophen (g)	4.6 ± 2.1	4.4 ± 2.4	4.3 ± 2.3	3.7 ± 1.9
Hydrocodone (mg)	46 ± 14	43 ± 19	41 ± 16	38 ± 13

Values are mean ± SD.

TENS = transcutaneous electrical nerve stimulation; PCA = patient-controlled analgesia; Mixed TENS = alternating frequency at 2 and 100 (2/100) Hz of TENS.

* $P < 0.05$, significantly different *versus* control.

† $P < 0.05$, significantly different *versus* 2 Hz.

‡ $P < 0.05$, significantly different *versus* 100 Hz.

ence did not account for the differences in the morphine requirements during the first 24 h after surgery. Analysis of PCA morphine usage in each 8-h period during the first 24 h demonstrated consistently greater opioid usage in group I than in the other three treatment groups, with the largest reduction occurring in group IV. As a result, the total dosage of morphine administered in the first 24 h was significantly decreased in groups II (45 ± 17 mg), III (44 ± 14 mg), and IV (31 ± 8 mg) compared with group I (61 ± 20 mg). In addition, significant less PCA morphine was required in group IV compared with groups II and III (table 2).

The total PCA amounts of morphine administered to patients in groups II (49 ± 8 mg), III (47 ± 15 mg), and IV (34 ± 11 mg) also were significantly decreased compared with group I (72 ± 25 mg), and there was a significant decrease in the overall amount of morphine required in group IV compared with all other groups (table 2). However, there were no differences in the need for supplemental "rescue" analgesic medication or in the amount of oral analgesics administered after discontinuation of PCA therapy among the four treatment groups (table 2).

In groups II, III, and IV, the incidences of both nausea (56%, 52%, and 52%, respectively) and pruritus (28%, 32%, and 24%, respectively) during the first 24 h were reduced compared with group I (nausea, 84%; pruritis, 60%). In addition, the incidence of dizziness during the first 24 h was only significantly reduced in group IV (32%) compared with group I (68%). During the 24- to 48-h interval after surgery, the incidences in groups II, III, and IV of nausea (12%, 11%, and 9%, respectively) and dizziness (32%, 24%, and 20%, respectively) were decreased compared with group I (nausea, 76%; dizziness, 64%). Although there were no statistically significant differences in nausea and pain visual analog scale scores during the first 24 h after surgery (table 3), groups II, III, and IV had significantly lower visual analog scale sedation scores than group I. In addition, there was a significant reduction in visual analog scale discomfort scores in group IV compared with group I.

On the follow-up pain assessment at the time of

Table 3. The Visual Analog Scale Scores before (Baseline) and at 24 h and 48 h after Surgery in the Four Treatment Groups

	Control (sham TENS)	2 Hz (low TENS)	100 Hz (high TENS)	2/100 Hz (mixed TENS)
Sedation				
Baseline	5 ± 7	5 ± 11	6 ± 12	4 ± 9
24 h	51 ± 27	32 ± 23*	30 ± 25*	28 ± 22*
48 h	29 ± 24	27 ± 26	24 ± 20	22 ± 19
Fatigue				
Baseline	12 ± 19	10 ± 21	9 ± 26	12 ± 17
24 h	48 ± 31	44 ± 28	42 ± 23	40 ± 30
48 h	31 ± 26	27 ± 18	26 ± 24	23 ± 20
Discomfort				
Baseline	8 ± 12	11 ± 14	7 ± 9	10 ± 13
24 h	46 ± 28	44 ± 32	40 ± 31	39 ± 23
48 h	32 ± 20	27 ± 18	24 ± 17	19 ± 14*
Pain				
Baseline	2 ± 6	3 ± 5	5 ± 7	4 ± 9
24 h	45 ± 26	43 ± 24	44 ± 27	41 ± 23
48 h	31 ± 25	28 ± 19	25 ± 23	24 ± 22
Nausea				
Baseline	3 ± 5	5 ± 4	2 ± 2	2 ± 4
24 h	28 ± 29	27 ± 26	25 ± 23	22 ± 25
48 h	19 ± 21	12 ± 14	14 ± 16	12 ± 17

Values are mean ± SD.

TENS = transcutaneous electrical nerve stimulation; Mixed TENS = alternating frequency at 2 and 100 (2/100) Hz of TENS.

* $P < 0.05$, significantly different *versus* control.

hospital discharge, five patients in group II complained that the electrical stimulation produced by the TENS device was uncomfortable, compared with one patient in groups III and IV. Eight patients in group IV, seven patients in group III, and seven patients in group II mentioned that the massage-like tapping ("soothing") effect of the TENS therapy provided additional comfort. Higher percentages of patients in groups II (72%), III (76%), and IV (80%) felt that the TENS device was helpful in the management of their postoperative pain compared with those in group I (24%). However, 16–20% of the patients in each of the four groups complained that the TENS adversely influenced their quality of sleep because of the presence of the cutaneous electrodes and wires. It is noteworthy that, compared with only 20% of the patients in group I, more than 75% of the patients in groups II, III, and IV expressed "a willingness to pay extra" to receive TENS therapy after a future operation.

Discussion

TENS is a useful supplemental (complementary) therapy for enhancing patient comfort after surgery; it is noninvasive, safe, simple, and devoid of systemic side effects.[1-3,10,11] Previous studies have reported variable effects of TENS therapy in reducing the amount of narcotic medication required postoperatively, as well as in decreasing the incidence of respiratory depression and sedation. Failure to standardize the location, intensity, timing, and frequency of the electrical stimulation with TENS therapy contributed to the variable results that have been reported in the medical literature. In a systematic review of the efficacy of TENS therapy in the management of acute postoperative pain, Carroll *et al.*[12] concluded that problems with randomization and failure to report treatment parameters (*e.g.*, location, time, intensity, and frequency of electrical stimulation) were found in 15 of 46 published studies examined.

In a recent study, Chen *et al.*[2] found that electrical stimulation of the incisional dermatomes was as effective as acupoint stimulation in reducing the PCA requirement and improving patient comfort after lower abdominal surgery, and both locations were more effective than either sham or nonacupoint stimulation sites. Wang *et al.* previously reported that the use of high-intensity (9- to 12-mA) stimulation was significantly more effective in decreasing the postoperative analgesic requirements than a low intensity (4–5 mA) of stimulation when used as an adjunct to PCA.[1] Furthermore, intermittent electrical stimulation for short intervals (30 min) has been found to be more effective than prolonged or continuous stimulation.[13] However, the effect of the frequency of the electrical stimulus on the analgesic response to TENS therapy had not been studied in the postsurgical setting. We designed a study to evaluate the relative effectiveness of different stimulus frequencies in reducing the postoperative PCA opioid requirement. Analogous to the findings of Hansson and Ekblom,[8] we found no difference between low- (2-Hz) and high-frequency (100-Hz) electrical stimulation. However, the alternating pattern of low- and high-frequency stimulation may offer an advantage over either frequency alone.

It has been reported that the effect of low-frequency TENS stimulation is mediated *via* proenkephalin-derived peptides acting on μ receptors, whereas high-frequency stimulation releases dynorphinergic-like substances, with the analgesic effects mediated *via* kappa opioid receptors.[14,15] In humans, low-frequency (2-Hz) transcutaneous acupoint electrical stimulation produced a marked increase (367%) in immunoreactive met-enkephalin-arg-phe from preproenkephalin, but not immunoreactive dynorphin A from preprodynorphin in lumbar cerebrospinal fluid samples.[14] In contrast, high-

frequency (100-Hz) TENS produced a 44% increase in immunoreactive dynorphin A, but no increase in immunoreactive met-enkephalin-arg-phe. In order to optimize the analgesic response, the use of alternating low- and high-frequency ("dense-disperse" mode) electrical stimulation has been recommended.[17] Han and Sun[18] reported that electrical stimulation using the dense-disperse mode (*i.e.*, mixed frequencies) produced differential release of met-enkephalin and dynorphins into the spinal fluid and suggested a synergistic effect with exogenously administered opioid analgesics. The current findings also suggest that periincisional stimulation utilizing mixed frequencies (2 and 100 Hz) also produces a significant reduction in the opioid medication requirement and side-effect profile.

The total number of PCA doses of morphine in the first 24 h after surgery was significantly reduced with mixed low- and high-frequency (2- and 100-Hz) stimulation compared with low (2-Hz) or high-frequency (100-Hz) stimulation alone. Compared with the control group, total PCA morphine dosages in all "active" TENS groups were decreased significantly in the first 24 h postoperatively and at the end of the 48-h study period. Although some studies have suggested that the analgesic effect of TENS therapy represents a pure "placebo effect,"[19,20] this study clearly demonstrates that the placebo effect cannot completely explain the beneficial action of the TENS therapy in this pain model.

Although it is difficult to design a true "control" for the electrical tapping sensation produced by the TENS device, use of a sham TENS device that appeared to be functioning "normally" but produced no perceptible electrical stimulation appeared to be a reasonable approach to this problem.[1,2,21] In order to "blind" the patient with respect to the treatment modality, patients were told that the investigators were studying the effect of TENS therapy on their level of pain after surgery and that they may or may not feel the tapping sensation produced by the TENS device. The single-blind, sham-controlled study design should have minimized the impact of patient bias on the study results. Although a double-blind study design would have been preferable, investigator bias was minimized by utilizing only objective data in the statistical analysis.

It has been suggested that TENS therapy produces a differential effect on incisional and "deep" pain after surgery. For example, Smith *et al.*[22] reported that TENS was significantly more effective in reducing cutaneous, movement-associated incisional pain than "deep" visceral pain after lower abdominal surgery. On the follow-up pain assessment, only 24% of the patients in the sham (control) group believed that the therapy decreased their pain. In contrast, 72%, 76%, and 80% of the patients in the 2-Hz, 100-Hz, and 2- and 100-Hz groups, respectively, felt that TENS therapy decreased their postoperative pain. Of note, about 30% of patients in the active TENS groups commented that the massage-like effect of TENS improved the quality of sleep and provided additional comfort. Over 75% of patients in the active TENS groups (compared with 20% in sham group) indicated that they would be willing to "pay extra" to receive TENS therapy after a future operation.

The duration of PCA therapy, as well as the incidence of opioid-related side effects such as postoperative nausea, dizziness, and itching were significantly reduced in the active TENS groups compared with the sham TENS treatment. In addition, the opioid-sparing effect may have contributed to a decrease in postoperative sedation in the mixed frequency group. The reduction in these common postoperative side effects may be the result of both the decreased opioid requirement, as well as an effect of improved pain control on postoperative nausea.[23] The similarity of the incidences of vomiting in the active TENS and control groups was probably related to the early and aggressive treatment of postoperative nausea with antiemetic drugs.

In conclusion, the use of TENS at alternating ("mixed") stimulation frequencies of 2 Hz and 100 Hz produced a significant opioid-sparing effect when utilized as an adjunct to conventional PCA therapy in patients undergoing lower abdominal surgery. The use of mixed-frequency stimulation was slightly more effective than either low- or high-frequency stimulation alone in decreasing the postoperative analgesic requirement and the incidence of opioid-related side effects.

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