

P6 acustimulation effectively decreases postoperative nausea and vomiting in high-risk patients

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Background. Electrical acustimulation can reduce postoperative nausea and vomiting (PONV). The primary purpose of this study was to investigate the effectiveness of acustimulation in relation to known risk factors for PONV. We also tested the secondary hypothesis that pre- or post-induction application of acustimulation results in differences in PONV reduction.

Methods. Two hundred women undergoing vaginal hysterectomy were enrolled in this prospective, observer-blind, randomized controlled trial. Patients received randomly for 24 h acustimulation ($n=101$), subdivided into groups of pre-induction ($n=48$) and post-induction ($n=53$), or sham stimulation ($n=99$), subdivided into groups of pre-induction ($n=49$) or post-induction ($n=50$). Nausea and vomiting/retching was recorded for 24 h after operation in the whole group and stratified by risk factors (female gender, non-smoker, history of PONV/motion sickness, and postoperative morphine usage).

Results. The incidence of PONV and need for rescue therapy was significantly lower in the acustimulation than in the sham group (PONV, 33% vs 63%, $P<0.001$; rescue therapy, 39% vs 61%, $P=0.001$). The risk ratio for acustimulation and PONV was 0.29 [95% confidence interval (CI) 0.16–0.52] and for rescue therapy, it was 0.38 (95% CI 0.21–0.66). Subgroup analyses according to the simplified risk score by Apfel and colleagues revealed a reduction in high-risk patients, that is, when three or four risk factors were present. Binary logistic regression analysis revealed that no history of PONV and usage of acustimulation were independent predictors for risk reduction of all PONV qualities. No significant difference in PONV reducing effects could be detected between pre- and post-induction.

Conclusions. Continuous 24 h acustimulation decreases PONV, particularly in patients at high risk.

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Postoperative nausea and vomiting (PONV) occurs in up to 30% of unselected patients and is the most frequent side-effect after anaesthesia.^{1, 2} Recent studies showed that stimulation at the P6 acupuncture point is associated with a decreased PONV incidence.^{3, 4} In another study, however, transcutaneous electrical stimulation at the P6 acupuncture point reduced only nausea but not vomiting after laparoscopic cholecystectomy.⁵ Furthermore, a recent report demonstrated that unilateral stimulation of the P6 acupuncture point reduced nausea in the early postoperative period while measuring neuromuscular block.⁶

However, no data are available on the effectiveness of acupuncture in different risk factor groups for PONV. Moreover, optimum timing of acustimulation is a matter of debate. Although it was suggested that preoperative vs postoperative acupoint stimulation made no difference in the incidence of PONV, one study showed the best effect in reducing PONV when stimulation was administered after surgery.⁷

We, therefore, performed an observer-blind, randomized, and controlled study to evaluate the effects of the P6 acupuncture point on the incidence of PONV. Specifically,

we tested the primary hypothesis that acustimulation results in PONV reduction that is dependent on known risk factors (female gender, non-smoker, history of PONV/motion sickness, and postoperative morphine usage). If this primary hypothesis was true, we tested the secondary hypothesis that pre- or post-induction application of acustimulation results in differences in PONV reduction due to patients' bias.

Methods

Sample size

We screened a total of 289 patients. Forty-eight patients did not meet the eligibility criteria because of an allergy to chrome/nickel, 19 patients refused to participate in the study, and eight patients were excluded because of other exclusion criteria. Therefore, a total of 214 patients were randomized. Fourteen patients were excluded afterwards because of a change in the surgical technique resulting in a final sample size of 200 patients.

Study design

For this single centre, prospective, randomized, observer-blind study, we obtained approval from the ethic committee of the University of Duisburg-Essen and patients' written informed consent before participation. Female patients older than 18 yr with an ASA class I–III were eligible if scheduled to undergo vaginal hysterectomy requiring general anaesthesia. Exclusion criteria were patients with a cardiac pacemaker or implanted cardioverter/defibrillator, patients at risk for malignant hyperthermia, patients with an allergy to nickel/chrome, and change in surgical technique. Patient characteristic and morphometric data and risk factors that may influence PONV (e.g. PONV history and smoking history) were collected before operation from the patients' records and by interviewing patients during the consenting procedure.⁸ Patients were randomly allocated to an acustimulation ($n=101$) group and to a sham acustimulation ($n=99$) group. These groups were further randomly subdivided into the following subgroups: (A) acustimulation before induction of anaesthesia ($n=48$), (B) acustimulation directly after induction of anaesthesia ($n=53$), (C) sham acustimulation before induction of anaesthesia ($n=49$), and (D) sham acustimulation directly after induction of anaesthesia ($n=50$), as determined by drawing a sealed envelope indicating treatment assignment. The investigators responsible for collecting data were blind to the treatments administered to the study patients.

Acustimulation was provided by a commercially available device, the ReliefBand[®]. The ReliefBand[®] is a non-invasive, FDA approved, portable (34 g), battery-powered (two 3 V lithium coin cells), watch-like acustimulation

device and capable of applying current at 31 Hz up to 35 mA gradable in five strengths. The skin contact surface has two flat metal electrodes through which electrical stimulation is applied transcutaneously. Both the active and sham ReliefBand[®] devices were applied in the anaesthetic induction room to the P6 acupoint on the dominant upper extremity, located ~2–3 cm proximal to the distal wrist crease between the tendons of the flexor carpi radialis and the palmaris longus.⁹ Sham ReliefBand[®] devices were prepared by inactivating the electrodes with a silicone cover, which was invisible for both patients and investigators. The ReliefBands[®] were activated (31 Hz, strength grade III) either before induction or directly after induction of anaesthesia dependent on patients' group assignment and remained *in situ* and active for 24 h after surgery.

A standardized anaesthesia regimen was followed. Premedication was done with midazolam 7.5 mg orally on the day of surgery. General anaesthesia was induced with propofol (1–2 mg kg⁻¹ i.v.), fentanyl (1 µg kg⁻¹ i.v.), and atracurium (0.5 mg kg⁻¹ i.v.), and was maintained by isoflurane 0.8–1.6% end-tidal in nitrous oxide (60–70%) at the discretion of the anaesthesiologist not involved in the study. All patients received morphine 0.1 mg kg⁻¹ during surgery 30 min before the end of the operation. Analgesic therapy with morphine was continued in the post-anaesthetic care unit (PACU). A rescue therapy of tropisetron 2 mg was administered to any patient who experienced an episode of moderate or severe nausea, an episode of vomiting, or who requested rescue medication.¹⁰

Data collection

Morphine and tropisetron administration was recorded for 24 h in the PACU and on the ward. Patients were evaluated for the occurrence of nausea, retching, vomiting, and pain by an investigator unaware of the patients' group assignments at the following intervals: 2 h in the PACU, and at 6 and 24 h according to recommendations for PONV trials.^{8 11 12} Nausea, vomiting, and retching were categorized (0, no episode; 1, at least one episode) and collected at 6 and 24 h after surgery. Vomiting was defined as expulsion of stomach contents and retching as an involuntary attempt to vomit but not productive of stomach contents.

Statistical analysis

All data are presented as mean (SD) until otherwise indicated. Parametric variables were compared using an unpaired Student's *t*-test. Categorical variables were compared using the χ^2 test. We used a binary logistic regression model to calculate odds ratios, 95% confidence intervals (CI), and *P*-values for the risk of PONV or the need of rescue therapy. Overall, PONV was defined as at least one episode of nausea, retching, or vomiting during

the observation time of 24 h. Rescue therapy was defined as at least one dosage of tropisetron during the observation time of 24 h. Logistic regression analysis was done in a stepwise backward fashion with the indicated variables as covariates. Differences were regarded statistically significant with an alpha error of <0.05 . All statistical analyses were two-sided and performed using SPSS, version 15.0 (SPSS, Chicago, IL, USA).

Results

Two hundred patients completed the study protocol. Patient and morphometric characteristics and factors likely to influence PONV were not significantly different in the acustimulation and sham groups as were intraoperative variables (Table 1). There was a significant difference between acustimulation and placebo patients for experiencing PONV (defined as at least one episode of nausea, retching, or vomiting during the observation time of 24 h). The incidence of PONV was significantly lower in the acustimulation group compared with the sham group. This was true for early PONV (up to 6 h, 33% vs 55%, $P=0.001$) and for late PONV (24 h, 33% vs 63%, $P<0.001$). Moreover, 41 patients (39%) in the acustimulation group required a rescue therapy compared with 64 patients (61%) in the sham group. This represented a risk ratio of 0.38 (95% CI 0.21–0.66, $P=0.001$) for the acustimulation group to require rescue therapy.

We next investigated whether established risk factors for PONV (female gender, non-smoker, history of PONV or motion sickness, and postoperative morphine requirement) as defined by Apfel and colleagues¹³ influence the effect of acustimulation (Fig. 1). Given that our study comprised women only and with all patients receiving postoperative morphine therapy, the lowest score, which could be achieved, was 2. We also calculated for every risk factor group, the relative risk reduction of P6 acustimulation and could show that acustimulation was effective on nausea in patients with three or four risk factors (relative risk reduction 50–65% for early and late nausea): acustimulation was also effective on retching/vomiting only when four risk factors were present (relative risk reduction 52–60%, Table 2).

Given the effectiveness of acustimulation therapy in preventing PONV, we investigated in a multivariate model which risk factor or method is most capable for PONV prevention. We also tested the hypothesis that differences in PONV reduction exist regarding whether acustimulation was started pre- or post-induction. Using a logistic regression analysis for the occurrence of nausea, vomiting/retching, or need of rescue therapy, we could show that only a history of motion sickness ($P=0.01$) and usage of acustimulation (pre-induction, $P=0.004$; post-induction, $P=0.006$) were independent predictors for risk reduction of nausea. For retching/vomiting, we could show that

smoking ($P=0.049$), history of PONV ($P=0.007$), and usage of acustimulation (pre-induction, $P=0.010$; post-induction, $P<0.001$) were independent factors for risk reduction (Table 3).

Both history of PONV ($P=0.03$) and motion sickness ($P=0.02$) increased and acustimulation both pre- ($P=0.034$) and post-induction ($P=0.001$) decreased the requirements for rescue treatment.

Discussion

In this study, we could show that acustimulation was effective to reduce the incidence of PONV in high-risk patients. We could also show that the PONV reducing effect was detectable in the early postoperative period (up to 6 h) and also in the late postoperative period (24 h). Interestingly, acustimulation was more effective in reducing nausea than retching and vomiting. The effectiveness of acustimulation for influencing nausea and vomiting is still a matter of debate. We could show an effective relative risk reduction of nausea with at least three risk factors, whereas acustimulation was significantly effective on the reduction of retching or vomiting when four risk factors were present (Table 2). Our study, therefore, supports studies from different groups showing better effects on nausea than on vomiting. In a preliminary report involving the postoperative use of the ReliefBand[®], Zarate and colleagues⁵ found a significant anti-nausea effect but failed to demonstrate a significant decrease in the incidence of emesis. These only partially positive findings were confirmed in a recent study by Arnerberger and colleagues⁶ using a nerve stimulator for acustimulation at the P6 point. Moreover, Rusy and colleagues¹⁴ found a reduction in nausea but not emesis in paediatric patients.

Our result may suggest that acustimulation reduced PONV in patients at high risk for PONV (when three or more risk factors for PONV were present). In the moderate risk group, that is, with only two risk factors, no clear treatment effect could be detected, either because acustimulation does not work in patients who are not at high risk or because of the lower incidence, the limited sample size, or both did not provide sufficient power to detect such an effect. This is of particular importance since our study group are at high risk for developing PONV in that patients undergoing hysterectomy have an increased risk for developing PONV.¹⁵ Moreover, we could show that acustimulation was effective for preventing PONV regardless of whether it was applied pre- or post-induction thus arguing against patients' bias.

In our study, we used acustimulation for a duration of 24 h after surgery. As PONV qualities remained at similar high levels for the observational period of 24 h in the sham group (Fig. 1), we believe that such a long duration of therapy is essential to effectively prevent PONV. Moreover, we focused on a single surgical procedure in women with all patients receiving postoperative morphine and we used a

Table 1 Patient characteristics, duration of surgery and anaesthesia, and risk scores for PONV. †Sum of risk factors (female gender, history of motion sickness or PONV, non-smoking status, and postoperative morphine therapy). *P*-value refers to Student's unpaired *t*-test. * χ^2 test for trend. Data are mean (range), mean (sd) or %

	All (n=200)	Acustimulation (n=101)	Sham (n=99)	<i>P</i> -value
Age (yr)	48.7 (29–83)	48.9 (29–83)	48.4 (31–79)	0.76
Height (cm)	164 (7)	164 (8)	165 (7)	0.48
Weight (kg)	70.1 (12.7)	69.5 (11.7)	71.9 (13.5)	0.20
Anaesthesia duration (min)	117 (38)	118 (40)	116 (37)	0.68
Surgical time (min)	91 (36)	92 (37)	90 (35)	0.73
Duration of acustimulation therapy (h)	25.6 (2.4)	25.5 (3.1)	25.6 (1.3)	0.72
Smokers (%)	33.5	35.6	31.3	0.31
History of motion sickness (%)	31.0	26.7	35.4	0.12
History of PONV (%)	36.0	33.7	38.4	0.29
Risk score for PONV (%)†				
2	18.0	19.8	16.2	
3	49.0	47.5	50.5	
4	33.0	32.7	33.3	0.65*

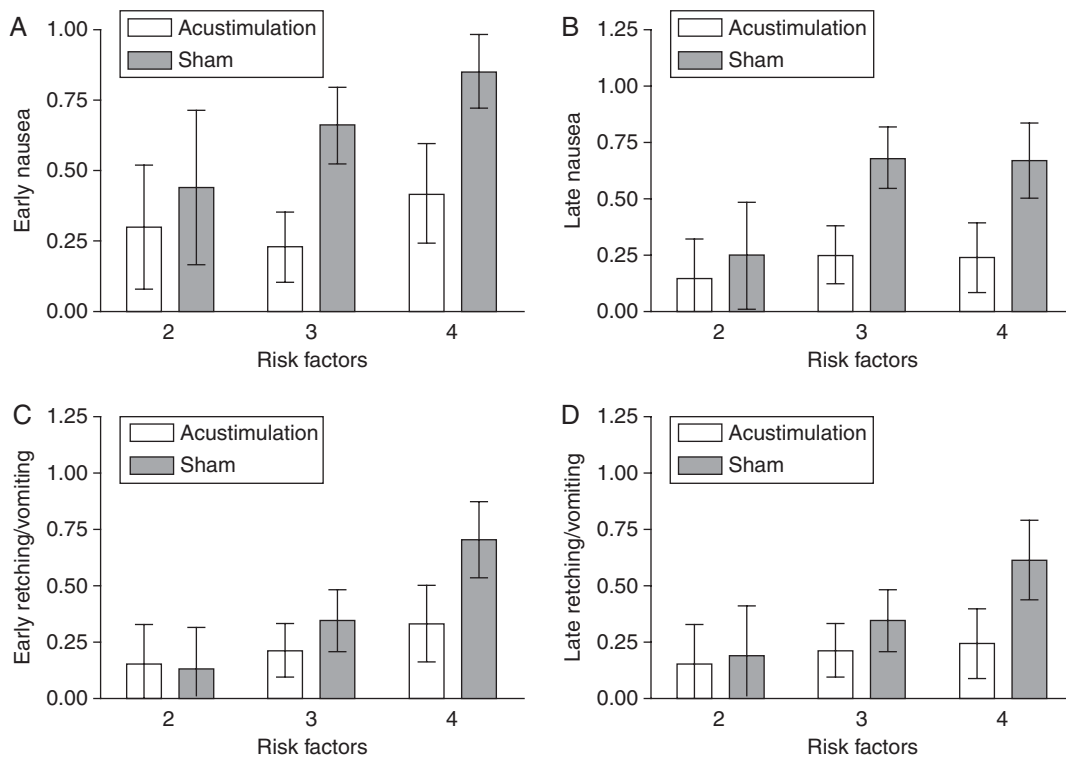


Fig 1 Effect of risk factors and acustimulation on the development of PONV. Risk factors were defined as: female gender, non-smoking, history of PONV or motion sickness, and postoperative morphine requirement. The fraction of patients suffering from early (up to 6 h) and late (after 24 h) is given. Data are presented as mean (95% CI).

Table 2 Relative risk reduction of acustimulation compared with sham acustimulation. Risk factors are defined as female gender, history of motion sickness or PONV, non-smoking status, and postoperative morphine therapy. RRR, relative risk reduction; OR, odds ratio; CI, confidence interval. *P*-values refer to χ^2 tests

Risk factors	6 h						24 h					
	Acu	Sham	RRR	OR	95% CI	<i>P</i> -value	Acu	Sham	RRR	OR	95% CI	<i>P</i> -value
Nausea												
2 (n=36)	30%	44%	31%	0.6	0.1–2.2	0.393	15%	25%	40%	0.5	0.1–2.8	0.451
3 (n=98)	23%	66%	65%	0.2	0.1–0.4	<0.001	25%	68%	63%	0.2	0.1–0.4	<0.001
4 (n=66)	42%	85%	50%	0.1	0.0–0.4	<0.001	24%	67%	63%	0.2	0.1–0.5	0.001
Retching or vomiting												
2 (n=36)	15%	13%	–20%	1.2	0.1–8.5	0.829	15%	19%	20%	0.8	0.1–4.4	0.764
3 (n=98)	21%	34%	39%	0.5	0.2–1.3	0.145	21%	34%	39%	0.5	0.2–1.2	0.145
4 (n=66)	33%	70%	52%	0.2	0.1–0.6	0.003	24%	61%	60%	0.2	0.1–0.6	0.003

Table 3 Logistic regression analysis for known risk factors and acustimulation on the development of PONV and the requirement of rescue therapy.
*Reference group

	Nausea		Vomiting/retching		Rescue therapy	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	0.99 (0.96–1.02)	0.544	0.99 (0.96–1.02)	0.396	0.98 (0.96–1.02)	0.389
Body mass index	0.95 (0.87–1.03)	0.204	0.98 (0.91–1.05)	0.533	0.96 (0.89–1.03)	0.278
Anaesthesia duration	1.01 (0.99–1.01)	0.458	1.00 (0.99–1.01)	0.482	1.01 (0.99–1.01)	0.278
Postoperative morphine use	0.99 (0.94–1.04)	0.657	0.97 (0.93–1.02)	0.278	0.97 (0.94–1.01)	0.193
Smoker						
No	1*		1*		1*	
Yes	0.70 (0.94–1.43)	0.333	0.53 (0.34–1.00)	0.049	0.73 (0.44–1.42)	0.370
History of PONV						
Yes	1*		1*		1*	
No	0.48 (0.23–1.01)	0.054	0.39 (0.19–0.77)	0.007	0.48 (0.24–0.93)	0.030
History of motion sickness						
Yes	1*		1*		1*	
No	0.34 (0.15–0.73)	0.010	0.69 (0.34–1.41)	0.310	0.42 (0.21–0.85)	0.016
Acustimulation						
Sham	1*		1*		1*	
Pre-induction	0.31 (0.14–0.68)	0.004	0.37 (0.18–0.79)	0.010	0.44 (0.21–0.94)	0.034
Post-induction	0.33 (0.15–0.73)	0.006	0.26 (0.13–0.56)	<0.001	0.28 (0.13–0.59)	0.001

standardized anaesthetic setting. Thus, relating to the risk score by Apfel and colleagues,¹³ these women by study design carried already two of four possible risk factors for developing PONV (because all patients were females and all required postoperative opioids). Patients with three or more risk factors benefited most from acustimulation therapy, whereas patients with only two risk factors showed no additional effect. Thus, it is not too surprising in retrospect that acustimulation may show smaller effects in study populations at less risk for PONV. Given the significance of the risk factors for developing PONV, we recommend to take into account these considerations in subsequent studies addressing potential effects of acustimulation.

Using a binary logistic regression model, we could show that acustimulation was independently associated with a reduction of PONV by up to 74% when PONV is classified as at least one episode of nausea, retching, or vomiting. Although we used the established risk factor system, which was established by Apfel and colleagues^{13 15} to evaluate which patients benefited mostly from acustimulation (Table 2), logistic regression analysis with each factor investigated separately revealed that history of PONV and history of motion sickness showed the biggest effect on the development of PONV, besides acustimulation. Therefore, one should have to keep in mind that the risk stratification score is only a simplified system and each risk factor might have different weight in influencing the predictability of development of PONV.

The relative risk reduction of 50–60% in our study with three or more risk factors is higher compared with other studies showing a relative reduction of PONV by 25%⁶ which is comparable with the effect of well-established drug treatments.^{16 17} Therefore, pre-selection high-risk patients may help to identify those who greatly benefit from acustimulation therapy.

Our study has limitations. Although both patients and investigators recording data were ‘blind’ as to the treatments assigned, patients receiving the active ReliefBand[®] devices pre-induction are more likely to be able to detect a tingling sensation potentially evoked at the P6 acupoint, and, therefore, patient bias may have contributed to the greater antiemetic efficacy of pre-induction acustimulation *vs* sham. However, this methodological problem is common to many clinical studies involving the use of non-pharmacologic antiemetic therapies and has been reported previously.^{4 18} Moreover, all patients were told that a tingling sensation, which was irrespective of the treatment assignment, may happen. Furthermore, different results might be obtained with other types of surgery or with other anaesthetic regimen. Regardless, acustimulation was effective in decreasing PONV irrespective of risk factors and morphine consumption. Finally, due to our limited sample size, we were not able to investigate interactions between risk factors and acustimulation therapy. To this end, factorial trials of sufficient sample size, similar to the previously designed and conducted studies by Apfel and colleagues,^{15 19} could shed light on that issue.

In conclusion, we could show that acustimulation by the ReliefBand[®] decreases PONV with best effects on nausea and in patients with three or more risk factors. Therapy duration of 24 h may be essential to effectively prevent PONV in high-risk patients, who markedly benefit from acustimulation therapy.

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