Effect of perioperative electroacupuncture as an adjunctive therapy on postoperative analgesia with tramadol and ketamine in prostatectomy: a randomised sham-controlled single-blind trial

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ABSTRACT

Objectives To study the analgesic effect of electroacupuncture (EA) as perioperative adjunctive therapy added to a systemic analgesic strategy (including tramadol and ketamine) for postoperative pain, opioid-related side effects and patient satisfaction.

Methods In a sham-controlled participant- and observer-blinded trial, 75 patients undergoing radical prostatectomy were randomly assigned to two groups: (1) EA (n=37; tramadol+ketamine +EA) and (2) control (n=38; tramadol+ketamine). EA (100 Hz frequency) was applied at LI4 bilaterally during the closure of the abdominal walls and EA (4 Hz) was applied at ST36 and LI4 bilaterally immediately after extubation. The control group had sham acupuncture without penetration or stimulation. The following outcomes were evaluated: postoperative pain using the Numerical Rating Scale (NRS) and McGill Scale (SF_MPQ), mechanical pain thresholds using algometer application close to the wound, cortisol measurements, rescue analgesia, Spielberger State Trait Anxiety Inventory (STAI Y-6 item), patient satisfaction and opioid side effects.

Results Pain scores on the NRS and SF_MPQ were significantly lower and electronic pressure algometer measurements were significantly higher in the EA group than in the control group (p<0.001) at all assessments. In the EA group a significant decrease in rescue analgesia was observed at 45 min (p<0.001) and a significant decrease in cortisol levels was also observed (p<0.05). Patients expressed satisfaction with the analgesia, especially in the EA group (p<0.01). Significant delays in the start of bowel movements were observed in the control group at 45 min (p<0.001) and 2 h (p<0.05).

Conclusions Adding EA perioperatively should be considered an option as part of a multimodal analgesic strategy.

INTRODUCTION

Acute postoperative pain remains a major clinical problem that affects patient recovery and quality of life, despite the considerable efforts of anaesthesiologists using multimodal analgesia with numerous combinations of drugs and techniques.1—7

Electroacupuncture (EA) is a technique that enhances the efficacy of classic acupuncture techniques and broadens its therapeutic application. It has been used as an adjunct for preoperative sedation because it decreases the use of opioids and other anaesthetic drugs intraoperatively for the treatment and management of postoperative pain and opioid adverse effects, especially the incidence of postoperative nausea and vomiting, and positive outcomes have been observed in most studies.5—8–20 A frequency of 100 Hz causes analgesia through serotonin and dynorphin secretion, which has a rapid onset and shorter duration.13 18 20 However, a frequency of 4 Hz causes analgesia through endorphin and met-enkephalin secretion and it exhibits opposite effects in onset and duration.13 18 20 In this study the EA technique...
was applied at acupuncture points (LI4 and ST36) that did not have any direct neurological segmental correlation with the prostate area, so the technique did not interfere with the surgical field.

Postoperative pain after radical prostatectomy is moderate to severe, self-limiting and short in duration (<48 h).\textsuperscript{21–23} This study investigated the efficacy of EA as an adjunctive perioperative treatment during the application of a multimodal systemic analgesic strategy such as tramadol and ketamine in patients undergoing radical prostatectomy and examined its effect on the incidence of opioid side effects and feelings of well-being.

**Study design**

**Study population**

Men aged 50–75 years, American Society of Anesthesiologists Physical Status 1–3, who were scheduled for radical prostatectomy were recruited to this prospective single-blind controlled trial and randomly divided into two groups using a computer-generated randomisation sequence: EA group (tramadol+ketamine+EA) and control group (tramadol+ketamine). The randomisation was concealed by the director of the anaesthesiology department. Further details are given in the online supplement.

The exclusion criteria were: patients receiving monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors; significant cardiovascular, pulmonary, renal or hepatic disease; epilepsy or a history of seizures; obesity (body mass index >35); chronic use of opioids or chronic pain, postoperative nausea and vomiting; cognitive dysfunction; not Greek-speaking; and previous treatment with acupuncture.\textsuperscript{5, 24}

**Protocol for anaesthesia and surgery**

Patients were informed preoperatively of the plan for postoperative analgesia and measurement of pain using the Numerical Rating Scale (NRS), Present Pain Intensity Scale (PPI), Short-Form McGill Scale (SF-MPQ) and the electronic pressure algometer function to assess the efficacy of EA. Participants were informed that the study compared EA plus tramadol+ketamine with tramadol+ketamine.

General anaesthesia was conducted by one of a team of five anaesthetists not involved in patient postoperative assessments.

All the patients underwent radical retropubic prostatectomy for prostate malignancy. The procedure involves removal of the prostate gland and pelvic lymph node dissection, and was performed with a midline extraperitoneal lower abdominal incision. Surgery was conducted by one of two surgeons.

**Analgesia**

All patients received 40 mg parecoxib intravenously 1 h before the end of surgery and 20 mg/kg paracetamol intravenously 30 min before. Both groups received an intravenous bolus of 1.5 mg/kg tramadol and 10 mg ketamine 30 min before the end of surgery. Administration was continued by intravenous infusion of 0.15 mg/kg/h tramadol and ketamine via an adjustable flow disposable pump (Paragon). The dose of ketamine was subanaesthetic and did not exceed 300 mg/24 h.\textsuperscript{25, 26} The 24 h tramadol dose did not exceed 600 mg.\textsuperscript{27}

Postoperatively, if the NRS scale was ≥3 or the PPI scale ≥2, the pain treatment was considered unacceptable. Tramadol (50 mg intravenously) was first administered to these patients and morphine (2 mg) was subsequently administered if the NRS scale did not decrease by at least two points after 30 min. This procedure could be repeated as necessary. The analgesic infusion was stopped if the patient exhibited a sedation score >2. The patient was reassessed in 1 h and the infusion was initiated with the same or decreased flow. If patients experienced acute pain any time during the 24 h following surgery, the physician called the anaesthetist and a new assessment took place.

**Intervention and control**

For the patients in the EA group, a certified acupuncturist placed the needles (Ener-Qi 0.26×25 mm) in LI4 at a depth of 20 mm in both hands\textsuperscript{28} when the closure of the abdominal walls was initiated. EA was applied for 30 min using an EA stimulator (ITO ES-160) and a constant pulse programme with a 300 μs duration and 100 Hz frequency. The needles were connected to the EA stimulator and secured to the skin with adhesive tape. Twitch of an adjacent muscle confirmed correct needle placement. The stimulator was then switched off and patients were awakened. EA was administered again at ST36 and LI4 for 30 min at a frequency of 4 Hz just after extubation. The electrodes were connected in pairs, ST36–ST36 and LI4–LI4.\textsuperscript{28} To overcome the interaction with the ECG monitor, monitoring was conducted by invasive arterial blood pressure (BP).

Patients in the control group had a sham acupuncture intervention. The needles were placed and secured by adhesive tape, without penetrating the skin, at the same points. The electrodes were connected to each other in pairs and the stimulator light was on, but no electrical current was applied. The same procedure was followed during surgery and after extubation as above. The patients in both groups were told that they may or may not feel an electrical current sensation.

The study was single blind because the patients were anaesthetised during the initial application of the EA intervention and the second application was performed just after awakening from anaesthesia. Therefore, the patients were unlikely to comprehend the technique although they were informed about it. Anaesthetists during the EA application knew the
group to which the patients belonged, although they did not deal with them postoperatively. An anaesthetist who was not involved with patients intraoperatively performed the assessments at standard time points (45 min, 2 h, 6 h, 12 h and 24 h after surgery). 18 29

Description of outcomes
A purpose-designed form was used to record the intensity of the patient’s pain using the NRS pain scale at rest and during movement (deep breath) with 11 levels of pain and the PPI scale with six levels of pain. Patient pain was assessed using the McGill pain scale (SF-MPQ) with four levels of pain at 6 h and 24 h postoperatively.

The electronic pressure algometer device (Wagner Pain Test FDIX Algometer, Greenwich, USA) was applied 2 cm on each side of the midline extraperitoneal lower abdominal incision. A 1 cm² digital probe was pressed perpendicularly to the skin, and patients reported the pain thresholds at the right and left sides of the incision in kg/cm² at standard time points following surgery. 29–32

The presence of opioid side effects such as nausea, vomiting, pruritus and bowel movements (auscultation intestinal sounds) was noted. The sedation score was assessed using a sedation scale with four levels of sedation (visual analogue scale 0–3). 33 Vital signs (BP, heart rate, respiratory rate) and rescue analgesia were also recorded.

Preoperatively and 24 h after surgery, the patients were asked to answer the Spielberger State Trait Anxiety Inventory (STAI Y-6 item), with gradations from 1 to 4. 34 35 Also, 24 h after surgery they were asked to answer ‘yes’ or ‘no’ to the following questions: “Did you sleep well?” and “Did you have nightmares or bad dreams?”, and by a 6-point Likert verbal rating scale to the question “Were you satisfied with your analgesic technique?” 36 37

Blood samples were drawn at time 1 (Cort1) at 08:00 on the day of surgery, time 2 (Cort2) 45 min following surgery and at time 3 (Cort3) at 08:00 on the first postoperative day. The cortisol concentration was then analysed by Fluorescence Polarisation Immunoassay and AxSYM reaction agent.

Data management and analysis
Based on a small pilot study (five patients per group), we performed a power analysis in order to determine the sample size that was required to obtain significant effects for each pain scale at 6 h following surgery. We calculated that 30 patients per group would be sufficient (using power=90% and type I error=5), and allocated 35 per group to anticipate withdrawals.

Linear modelling methodology was used for the analysis of repeated measures of quantitative data. Sidac post hoc methodology was carried out for p value adjustment. The χ² test was applied for the comparison of proportions, while the t test was used for the comparison of baseline characteristics of continuous measurements. Data in the Likert scales were considered quantitative. The Shapiro–Wilk test was used to assess normality assumptions.

The results are reported as mean±SD and 95% CIs are also reported where appropriate. p Values <0.05 were considered statistically significant. IBM SPSS Statistics V19.0.0 (SPSS, Chicago, Illinois, USA) was used for statistical analyses.

RESULTS
A total of 75 patients were included in the trial. Three patients from the control group and two patients from the EA group were excluded during the study, so a total of 70 patients completed the study with 35 in each group (figure 1). The study lasted from January to December 2012.

The baseline demographic and clinical characteristics of the patients are shown in table 1.

Pain scores on the NRS at rest and during movement, on the PPI scale and on the SF_MPQ showed that both groups exhibited significant decreases in pain intensity during the test period (p<0.001; figures 2 and 3).

The application of the electronic pressure algometer showed that both groups had a significant increase in the pain threshold overall during the test period (p<0.001). Specifically, both groups exhibited a significant increase in pain threshold on the right side of the incision (p<0.01), but this was not observed on the left side of the incision (p>0.05; figure 4).

Study of the vital signs showed that both groups exhibited significant improvement in these measurements during the study (p<0.001). Both groups had similar systolic BPs (p>0.05), heart rates (p>0.05) and respiratory rates (p>0.05) but different diastolic BPs (p<0.01; see online supplement).

A small percentage of patients reported adverse effects of opioid analgesics, with no significant differences between the groups except for the absence of bowel movements (table 2). None of the patients reported any sleep disturbance or insomnia in either group. Only a small number of patients reported nightmares postoperatively and no significant differences were observed between the groups. Only seven patients in the control group and four in the EA group reported sleeplessness and one patient from each group reported nightmares.

A significant decrease was detected in rescue analgesia in the EA group at 45 min (p<0.001) and in the total amount of analgesia (p<0.001).

During the whole study neither group showed significant changes in cortisol levels (p>0.05), but there were differences between the groups. The values of Cort3 varied significantly between the two groups compared with Cort1 (p<0.01). A significant decrease in cortisol levels was observed in the EA
group for Cort3 (14.37±9.18) versus Cort1 (17.01 ± 5.42) measurements (p<0.05; see online figure S1).

On the STAI Y-6 item assessment, the total score of six items showed no differences between the two groups during postoperative assessments (p>0.05) nor between the preoperative and postoperative assessments within each group (EA, p>0.05; control, p>0.05). However, significant differences between groups were observed in the partial assessments of each parameter (see online supplement).

All the patients reported that they were satisfied with the analgesic technique used, but a significant difference was observed between the groups (p>0.01) with the EA group showing superiority.

DISCUSSION
In this study, 91.4% of the patients in the EA group reported no pain while relaxing (NRS ≤3) at 45 min and 2 h following surgery, whereas the percentages in the control group at these time points were 45.7% and 60%, respectively. Analgesia was reported as satisfactory by patients in the EA group on movement at 45 min (91.4%) and 2 h (82.8%) following surgery,

Table 1 Perioperative data

<table>
<thead>
<tr>
<th></th>
<th>EA group</th>
<th>Control group</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>67.3±6.3</td>
<td>65.5±5.6</td>
<td>0.214</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>83.9±11.9</td>
<td>81.2±12.3</td>
<td>0.354</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.7±3.8</td>
<td>27.9±3.8</td>
<td>0.464</td>
</tr>
<tr>
<td>ASA PS (1/2/3)</td>
<td>5 (14.2%)/28 (80%)/2 (5.7%)</td>
<td>6 (17.1%)/24 (68.5%)/5 (14.2%)</td>
<td>0.734</td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (60%)</td>
<td>21 (60%)</td>
<td>0.995</td>
</tr>
<tr>
<td>Heart disease</td>
<td>5 (14.2%)</td>
<td>7 (20%)</td>
<td>0.672</td>
</tr>
<tr>
<td>Diabetes mellitus type I</td>
<td>2 (5.7%)</td>
<td>6 (17.1%)</td>
<td>0.390</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>2 (5.7%)</td>
<td>3 (8.5%)</td>
<td>0.832</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>161.4±51.5</td>
<td>137.7±54.3</td>
<td>0.065</td>
</tr>
<tr>
<td>Duration of anaesthesia (min)</td>
<td>189.0±52.4</td>
<td>163.7±58.5</td>
<td>0.060</td>
</tr>
<tr>
<td>BIS (mean)</td>
<td>48.2±0.4</td>
<td>48.2±2.4</td>
<td>0.970</td>
</tr>
<tr>
<td>Remifentanil (µg)</td>
<td>1003.6±522.7</td>
<td>1041.9±631.9</td>
<td>0.783</td>
</tr>
<tr>
<td>Tramadol sum (mg)</td>
<td>443.7±67.4</td>
<td>461.5±63.2</td>
<td>0.257</td>
</tr>
<tr>
<td>Ketamine sum (mg)</td>
<td>289.8±18.5</td>
<td>281.2±23.5</td>
<td>0.136</td>
</tr>
<tr>
<td>Paracetamol (mg)</td>
<td>1637.9±349.1</td>
<td>1641.4±241.1</td>
<td>0.960</td>
</tr>
</tbody>
</table>

Data presented as mean±SD or n (%).

ASA PS, physical status according to the American Society of Anesthesiologists; BMI, body mass index; BIS, bispectral index; EA, electroacupuncture; hypertension, if patients had a history of hypertension and they were administered medication.

DISCUSSION
In this study, 91.4% of the patients in the EA group reported no pain while relaxing (NRS ≤3) at 45 min and 2 h following surgery, whereas the percentages in the control group at these time points were 45.7% and 60%, respectively. Analgesia was reported as satisfactory by patients in the EA group on movement at 45 min (91.4%) and 2 h (82.8%) following surgery,
and in the control group by 31.4% and 48.5%, respectively. EA significantly decreased the pain intensity, as measured by several pain scales, mechanical pain thresholds after algometer application and rescue analgesia. Patients' mood and optimism also improved, as assessed using STAI Y-6 item, and they were satisfied with the applied analgesic technique. Cortisol levels increase during significant stressors such as acute clinical pain. The cortisol levels in the EA group tended to decrease in this study from the preoperative to the first postoperative day assessment, but these levels tended to increase at the same assessments in the control group. However, cortisol levels are highly variable and require a larger sample to show significant differences. The results of cortisol measurement in the literature are inconsistent.

The incidence of adverse effects to opioids was generally low in both groups in the present study due to EA using a multimodal analgesia model.

The selected points ST36 and LI4 were easily accessed for needle placement during the surgery and their correct placement was certified by the contractions of the adjacent muscles after the application of EA, despite the loss of the de qi sensation. Nausea and vomiting, which are significant problems of opioid use, occurred in a small number of patients. The incidence of pruritus was clinically very low overall. On the other hand, the incidence of sedation was more frequent in the control group at 45 min (20% of patients) and occurred in only one patient in the EA group. Bowel movements were not delayed in either group and appeared early, with statistically significant differences at 45 min and 2 h after surgery. The incidence of urinary retention could not be evaluated because urinary catheterisation was performed.

The limitations of this study were reduced as much as possible by comparing patients who underwent the same operation by the same team of surgeons and anaesthesiologists and the EA was applied by a specific certified experienced anaesthesiologist. The major problem in analysing acupuncture studies is the definition of a control group with placebo and sham acupuncture and the blinding. In this study the anaesthesiologists and the acupuncturist knew when EA was applied although they did not deal with patients postoperatively as assessments were performed by a blinded anaesthetist. On the other hand, the patients probably did not comprehend the technique because they were anaesthetised during the initial application of the EA intervention and the second application was performed just after extubation. The use of adhesive tapes on all acupuncture sites of all patients was also designed to ensure that neither the patients nor the staff caring for them knew which treatment was given to each patient. Also, we could ask patients afterwards if they understood to which group they belonged. The measurements could have been continued for an additional 24 h.

Evidence exists for the value of EA in the perioperative period for the treatment and management of postoperative pain and adverse opioid effects. Wang et al reported that acupuncture was more efficient in surgical patients if administered postoperatively. Lin et al concluded that the optimal time for acupuncture has been shown to be the time immediately after surgery rather than before surgery or 2–4 h afterwards. The effect of each EA session only lasts approximately 2–3 h, which was confirmed in this study as a significant difference in the first two assessments (45 min and 2 h) was observed in the EA group (p<0.001). Sun et al reported that opioid consumption and postoperative pain intensity were significantly decreased in the acupuncture group compared with a control group, but there was no significant difference if the technique was applied before or after the operation. They also showed a significant reduction in the incidence of opioid-related adverse effects.

The selected points ST36 and LI4 were easily accessed for needle placement during the surgery and their correct placement was certified by the contractions of the adjacent muscles after the application of EA, despite the loss of the de qi sensation.
Apart from the Chinese literature, Hollinger et al.\textsuperscript{28} used LI4 points bilaterally during surgery and reported no cardiac fibrillation. In the present study the patients were monitored with invasive arterial pressure recording and none developed arrhythmias. The patients did not display any adverse effects such as immediate haemorrhage or pain after 3 months. None of the patients reported injury to the peripheral nerves, capillaries or muscle fibres.\textsuperscript{20, 36, 44, 45} Three children developed adductor muscle fibrosis and adduction deformity of the thumb as a result of local vascular and muscular injuries from needling at the LI4 point in a previous study.\textsuperscript{45}

The addition of ketamine during postoperative analgesia treatment is controversial.\textsuperscript{25, 26, 46, 47} Various studies have shown that a subanaesthetic dose of ketamine at 24 h decreases postoperative morphine consumption after major surgery with a lower incidence of side effects such as nausea or vomiting and without an increase in psychotic disorders.\textsuperscript{5, 6, 17, 25, 26, 46, 48, 49} No psychomimetic effects were observed using low-dose ketamine, which contrasts with patients under general anaesthesia who receive benzodiazepines.\textsuperscript{25, 26} The results of this study confirm these earlier studies. It is also worth noting that the addition of ketamine prevents remifentanil-induced hyperalgesia.\textsuperscript{45}

Although the treatment of acute postoperative pain is part of the daily routine for anaesthesiologists, many people still experience it.\textsuperscript{51, 52} Improved collaboration between those involved in postoperative analgesia is recommended. The characteristics of the patient, type of surgery, previous experience of acute and chronic pain and its treatment should be considered and the early rehabilitation of patients and the combination of analgesics for multimodal analgesia should be investigated using well-organised prospective randomised double-blind controlled trials.\textsuperscript{2–4, 7, 53} Moreover, as White et al.\textsuperscript{24} reported, it is time to “roll up our sleeves and get back to work” doing high-quality clinical research rather than simply reanalysing previously published studies.

In conclusion, the use of EA as adjunctive therapy in combination with tramadol plus ketamine perioperatively decreased postoperative pain in patients undergoing radical prostatectomy. The adverse effects of opioids were also reduced and the patients were more positive with improved feelings of well-being.

**Summary points**

- EA was evaluated as an adjunct to ketamine and tramadol for postoperative pain.
- EA was compared with sham EA in 75 patients undergoing radical prostatectomy.
- Patients in the EA group experienced significantly less pain and more rapid recovery of bowel movement.

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**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** The Ethics and Deontology Committee of the Aristotelian University of Thessaloniki Greece and the Scientific Committee of the General Hospital of Thessaloniki Greece ‘G. Gennimatas’ approved the study, which was registered with ClinicalTrials.gov (number NCT01526525).

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