

# Effect of Transcutaneous Acupoint Electrical Stimulation on Urinary Retention and Urinary ATP in Elderly Patients After Laparoscopic Cholecystectomy: A Prospective, Randomized, Controlled Clinical Trial

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**Purpose:** To investigate the effect of transcutaneous electrical acupoint stimulation (TEAS) on urinary retention after laparoscopic cholecystectomy in elderly patients, and to explore the relationship between TEAS and urinary ATP.

**Patients and Methods:** The TEAS group was administered active TEAS at specific acupuncture points prior to induction of anesthesia and continued for 45 mins after surgery. In the control group, participants received sham stimulus at the same acupoints and no output current was delivered by disconnecting the device's output line. Urine samples were collected and evaluated in the first spontaneous voiding after surgery. In this study, postoperative urinary retention (POUR) was the primary outcome, which was diagnosed based on clinical symptoms, ultrasound assessments, and the need for bladder catheterization. Secondary outcomes include urinary ATP, postoperative spontaneous urination, urination symptoms, catheter-related bladder discomfort (CRBD), delirium, duration and hospitalization costs.

**Results:** The study involved 598 patients recruited and randomized between August 2018 and June 2020. Among these patients, 547 (91.5%) completed the study and were analyzed. There were 64 cases of POUR, including 23 (8.4%, 95% confidence interval [CI]: 6.4–9.9%) in the TEAS group and 41 (15.0%, 95% CI: 9.3–13.4%) in the control group ( $p = 0.017$ ). A significant difference was observed between the TEAS and control groups for urinary ATP concentration in the first spontaneous urine postoperatively (344 nmol/L versus 233 nmol/L,  $p = 0.001$ ). There was a shorter spontaneous voiding recovery time, smaller voiding threshold, less postoperative catheterization, less CRBD, and lower hospitalization costs in TEAS group compared with control group.

**Conclusion:** TEAS reduces the incidence of POUR in elderly patients undergoing laparoscopic cholecystectomy, which may be related to an increase in bladder ATP release.

**Keywords:** transcutaneous electrical acupoint stimulation, urinary retention, ATP, catheterization, laparoscopic surgery, catheter-related bladder discomfort

## Introduction

Urinary retention is a common complication after anesthesia, often accompanied by painful vesical distention and cardiovascular responses, and can lead to motility and atony problems, especially in older patients.<sup>1,2</sup> In addition, in the elderly, urinary retention is associated with restlessness, confusion, and the possibility of delirium.<sup>3</sup>

In general anesthesia, stress responses are attenuated and sympathetic nerve activity is inhibited, as well as vagus nerve activity is inhibited.<sup>4</sup> As a result of reduced parasympathetic activity, baroreceptor function may be

impaired and the recovery of spontaneous urination may be delayed.<sup>5</sup> Aging is a physiological process associated with dysfunction of the autonomic nervous system.<sup>6,7</sup> The physiological response to anesthesia may be unpredictable and paradoxical if the autonomic nervous system is dysfunctional. ATP, the principal messenger released from urothelial cells, is a co-transmitter together with noradrenaline in sympathetic nerves and acetylcholine in parasympathetic nerves and considered a potential therapeutic target for functional bladder functional disorders.<sup>8</sup>

In recent years, acupuncture has gained popularity as a method of improving urination control. Acupuncture and related methods have been shown to reduce the incidence of urinary retention after orthopedic, obstetric and gynecological, and gastrointestinal procedures.<sup>9–11</sup> Transcutaneous electrical acupoint stimulation (TEAS), which applies electrical stimulation to acupuncture points instead of needles, has shown benefits in studies relating to regulating voiding, but remains controversial when used in elderly patients.<sup>12,13</sup> In addition, the effect of TEAS on urinary ATP function in patients following surgery is unclear. Therefore, we conducted a double-blind randomized trial and hypothesized that TEAS is effective in reducing urinary retention following laparoscopic cholecystectomy and is associated with increased urinary ATP release.

## Materials and Methods

### Design

The study was approved by the ethics committee of Tianjin Nankai Hospital and is in accordance with the Helsinki Declaration. The trial was registered at ClinicalTrials.gov (registration number: NCT03631160). Written informed consent was obtained from all participating patients prior to randomization.

### Patients

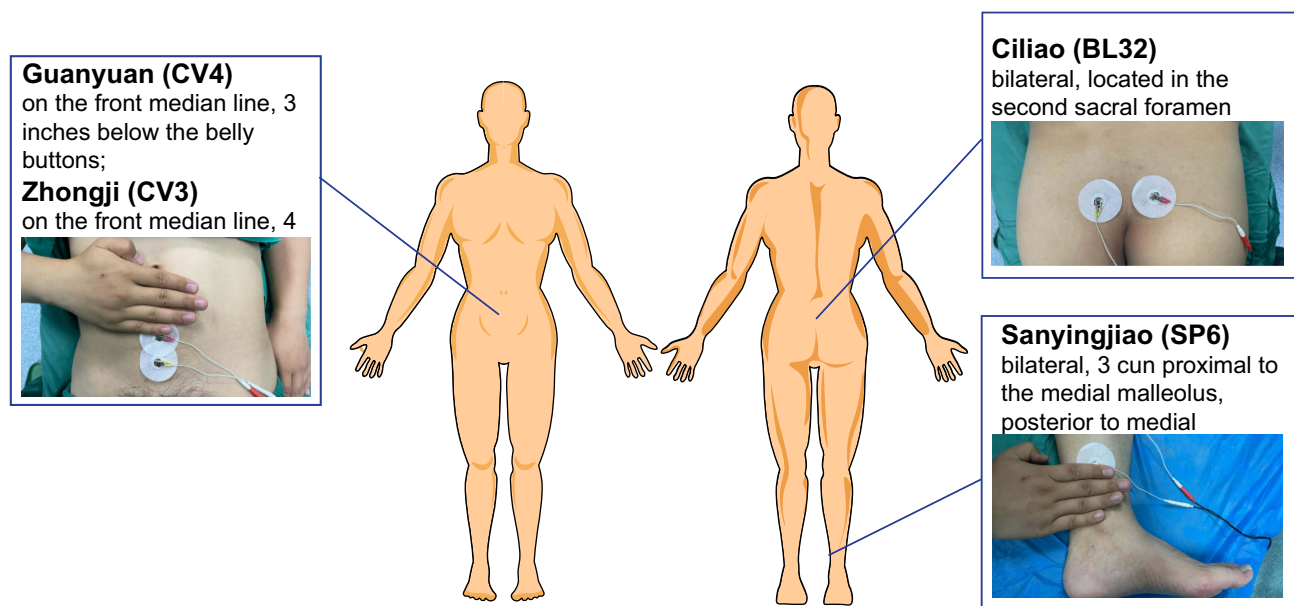
Inclusion criteria were: (1) age above 65 years; (2) elective laparoscopic cholecystectomy under general anesthesia; (3) no preventive or intraoperative indwelling catheter. The criteria for exclusion were: (1) urinary tract obstruction or infection, such as moderate or severe benign prostatic hyperplasia (International Prostate Symptom Score (I-PSS) greater than 7), urinary tract infections in the last 3 months; (2) contraindications for TEAS such as skin allergy, infections, itching or pacemaker wear; (3) previous experience with multiple acupuncture sessions; (4) preoperative American Society of Anaesthetists (ASA) grade  $\geq$  IV; (5) severe impairment requiring kidney replacement therapy; and (6) participation in other clinical investigations within 3 months.

Eligible participants were randomly assigned to the TEAS and control groups at a 1:1 ratio using block randomization. Random numbers were then sealed in sequentially numbered, opaque envelopes which were revealed by the acupuncture before administration. Participants, outcome assessors and statisticians were blinded to the treatment allocation.

### TEAS Administration

Four acupoints were selected as the stimulation points: Ciliao (BL32, bilateral), Sanyinjiao (SP6, bilateral), Zhongji (CV3), and Guanyuan (CV4). The above acupoints are located in lower back, lower leg and lower abdomen. Their positioning is based on the National Standard of the People's Republic of China: acupoint position (Figure 1). TEAS was administered by a licensed acupuncturist with  $\geq 8$  years of clinical acupuncture experience. A low-frequency pulse electroacupuncture stimulator (Hwato brand model no. SDZ—IV, Suzhou Medical Appliances Co., Ltd, Suzhou, China) was attached to the selected acupoints. Stimulus started 30 mins before induction of anesthesia and lasted 45 mins after surgery. The frequency of stimulation was 4 / 20 Hz, and the intensity was determined by the patient's tolerance until the local skin twitches slightly and the pain was tolerable.<sup>14</sup>

Participants in the control group received sham stimulus at the same points with sham electrode lines, cutting off output wires, causing no current output to pass to the patient, despite being connected. We also informed each patient that they may not feel tingling in their lower extremities and lower back when the stimulator works prior to stimulation. In addition, in order to make the simulation as realistic as possible, the stimulator with sham



**Figure 1** Location of acupoints in the trial.

electrode lines had the same working power indicator and sound as the normal electrode lines, indicating that the stimulator was effective even if it does not actually have an electrical current output.

## Anesthetic and Surgical Procedure

All patients were completely emptied before entering the operating room. The method of anesthesia was standard for the two groups. Anesthesia was induced with 0.2–0.6 mg/kg etomidate and 0.2–0.5 µg/kg sufentanil and maintained with remifentanyl and propofol infusion. Intraoperative monitoring included an electrocardiogram, noninvasive blood pressure, peripheral capillary oxygen saturation, carbon dioxide division at the end of breathing, and the bispectral index. Intra-abdominal pressure was maintained between 8–12 mmHg. Patients were treated with Ringer's lactate solution infusion at a rate of 10 mL/kg/h before and during the procedure. This was continued after surgery until oral fluid intake was allowed. Patient controlled intravenous analgesia (PCIA) with sufentanil combined with flurbiprofen was administered for 24–48 h postoperatively, as necessary.

## Data Collection and Urinary ATP Measurements

The primary outcome was the incidence of POUR after surgery in this study. Based on clinical symptoms, ultrasound assessments, and bladder catheterization requirements, postoperative urinary retention (POUR) was diagnosed by the attending surgeon ([Supplementary Table S1](#)).<sup>2</sup>

The secondary outcomes included urinary ATP concentration, spontaneous voiding ability, urination symptoms (such as voiding difficulty, oliguria, or nocturia), Catheter-related bladder discomfort (CRBD), delirium, early ambulation, length of hospital stay, and hospital costs. CRBD was evaluated by the anesthesiology resident: none = no complaints of CRBD symptoms, mild = reported only upon direct inquiry, moderate = spontaneous complaints by the patient without behavioral responses (eg, pulling out the catheter, flailing limbs, or a loud vocal response), and severe = spontaneous complaints by the patient with behavioral responses.<sup>15</sup> An assessment of postoperative delirium was made by trained personnel using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) and the Richmond Agitation-Sedation Scale (RASS) from the first to the third postoperative day.<sup>16</sup> A patient was considered delirious if he or she was awake (RASS of 3 or greater) and positive for CAM-ICU on either of the CAM-ICU assessments. Early ambulation was defined as any partial

or full weight-bearing activity conducted two to three times outside the ward, with a total walking distance of 250 to 500 m.<sup>17</sup>

During the first spontaneous void after surgery, urine samples were collected from thirsty patients in each group and tested for urinary ATP levels. The urine samples were centrifuged at 2500 x g for 5 minutes and stored at -80°C. Measurement of urine ATP concentrations was performed using a luminometer and a luciferin-luciferase assay (Sigma–Aldrich). In brief, the colorimetric reaction absorbance was measured using a spectrophotometer at 460 nm, and the ATP concentration was estimated by applying the luminescence value to a standard curve of known ATP concentrations.

## Statistical Analysis

We conducted all analyses using IBM SPSS 22.0 (IBM Corp., Armonk, NY, USA). Kolmogorov–Smirnov was used to test the normality of continuous data ( $p < 0.05$ : reject normality), with the mean and SD reported for normal data, and the median (IQR) for non-normal data. As appropriate, *t*-tests or Mann–Whitney *U*-tests were used to compare the two groups. Categorical variables were analyzed through the chi-squared test or Fisher's exact probability test and summarized as numbers (%). Statistical significance was set at  $p < 0.05$ .

## Results

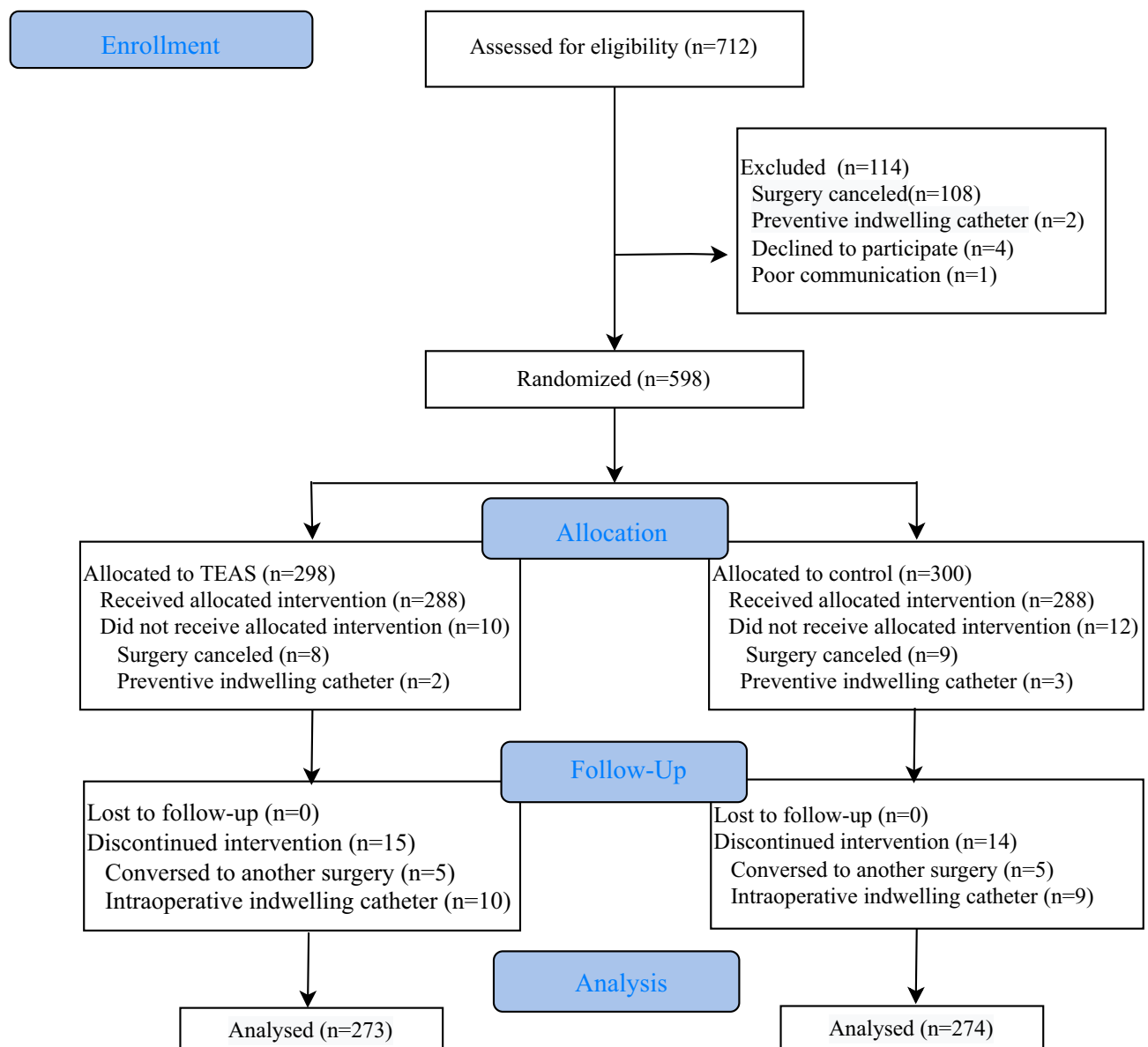
The study assessed 712 patients who underwent elective laparoscopic cholecystectomy, of whom 598 met the inclusion/exclusion criteria. The 598 patients were enrolled and randomly assigned to two groups, the TEAS group ( $n = 298$ ) and the control group ( $n = 300$ ). There were 22 subjects who did not receive allocated intervention due to cancellation of surgery or preventive indwelling catheter (10 subjects from the TEAS group and 12 subjects from the control group); 29 subjects discontinued interventions due to another surgery or an intraoperative indwelling catheter (15 subjects from the TEAS group and 14 subjects from the control group). This resulted in the analysis of data on 547 subjects, including 273 patients in the TEAS group and 274 patients in the control group. A detailed patient flowchart is shown in Figure 2.

As can be seen in Table 1, the demographics and baseline characteristics of the patients were similar between the two groups and no significant differences were observed between the two groups ( $p > 0.05$ ).

Sixty-four patients were diagnosed with POUR, including 23 (8.4%, 95% confidence interval [CI]: 6.4–9.9%) in the TEAS group and 41 (15.0%, 95% CI: 9.3–13.4%) in the control group with a statistically significant difference ( $p = 0.017$ , Table 2). As compared to the control group, patients in the TEAS group had a shorter recovery time from spontaneous voiding (5.1 h versus 8.1 h,  $p = 0.005$ ) and smaller voiding threshold (414.9 mL versus 504.8 mL,  $p = 0.048$ ). The concentration of urinary ATP was measured in the first spontaneous urine postoperatively, and the results showed that patients in the TEAS group had a significantly higher level of ATP concentration (387.6 nmol/L versus 244.5 nmol/L,  $p = 0.001$ ) than those in the control group (Figure 3).

As compared with the control group, there were fewer patients in the TEAS group who experienced voiding difficulty (22.3% versus 47.1%,  $p < 0.001$ ) and nocturia (22.7% vs 35.8%,  $p = 0.001$ ). Postoperative catheterization was less common in the TEAS group (8.4% versus 15.0%,  $p = 0.017$ ) and CRBD was less prevalent (0.7% versus 3.3%,  $p = 0.031$ ) in comparison to the control group, and fewer patients in the TEAS group demonstrated agitated behavior including attempts to pull out the catheter, flailing limbs, or loud vocalizations (0 versus 1.5%,  $p = 0.045$ ). The TEAS group had lower hospitalization costs compared to the control group (23,981.1 yuan [IQR: 20,644.1–30,114.3 yuan] versus 25,904.1 yuan [IQR: 21,679.4–34,155 yuan],  $p = 0.008$ ). While no significant differences were observed between the two groups in terms of delirium ( $p = 0.317$ ), vomiting ( $p = 0.750$ ), or hospitalization duration ( $p = 0.129$ ).

During the study, six patients experienced adverse events, including four cases of gross hematuria or lower urinary tract infection and two cases of localized acupuncture point redness or pruritus, and no statistically significant difference was found between the TEAS and control groups in terms of the above adverse events (Table 3). There were no serious adverse events reported in either group. And all adverse events occurring during the trial were mild and resolved within a short period of time.



**Figure 2** Patient flow chart.

## Discussion

According to our findings, TEAS can reduce the incidence of urinary retention in elderly patients following laparoscopic surgery. This mechanism may be related to the improvement of spontaneous urination reflex recovery by increasing ATP release, which is consistent with the hypothesis we presented.

POUR is defined as the inability to void when the bladder is full, along with pain and discomfort in the lower abdomen.<sup>2</sup> The incidence of POUR in the general surgical population varies widely. It is estimated to be 6–10% in laparoscopic cholecystectomy.<sup>18,19</sup> In older patients, changes resulting from physiological aging, as well as comorbidities and multiple drug therapies, may result in lower urinary tract symptoms, such as urinary retention and incontinence. The risk of POUR increases with age, with patients over 60 years of age being at double the risk.<sup>20</sup> In this population of elderly patients with poor mobility and cognitive impairment, combined with susceptibility to both infection and urinary bacterial overgrowth, a high rate of urinary tract infections is prevalent.<sup>21</sup> According to a three-year surveillance study of 134,637 patients, urinary tract infections are the second most common healthcare-associated infections among the

**Table 1** Baseline Participant Characteristics

Characteristic	TEAS Group (n=273)	Control Group (n=274)	p-value
Sex			0.820
Male	107(39.2)	110(40.1)	
Female	166(60.8)	164(59.9)	
Age, mean (SD), y	68.7(3.0)	68.7(3.0)	0.951
Height, mean (SD), cm	164.1(7.6)	165.4(8.2)	0.051
Weight, mean (SD), kg	67.54(11.3)	68.6(10.4)	0.24
BMI, mean (SD)	25.0(3.6)	25.0(3.3)	0.911
Creatinine	69.9(19.7)	70(19.2)	0.714
Coexisting medical conditions			
Hypertension	149(54.6)	140(51.1)	0.414
Diabetes mellitus	62(22.7)	59(21.5)	0.740
Current smoker	44(16.1)	50(18.2)	0.509
Alcohol use	19(7.0)	20(7.3)	0.877
Preoperative preparation			
Enema	125(45.8)	127(46.4)	0.895
Fasting	20(7.3)	19(6.9)	0.859
Surgical characteristics			
Operative time, median (IQR), h	0.9(0.6–1.2)	0.9(0.7–1.2)	0.685
Intravenous fluid, median (IQR), mL	750.0(700.0–800.0)	750.0(700.0–850.0)	0.839
Blood loss, median (IQR), mL	50.0(50.0–50.0)	50.0(30.0–50.0)	0.729
Intraoperative opioid dosage, intravenous morphine equivalents, median (IQR), mg	30.0(25.0–30.0)	30.0(25.0–35.0)	0.180
PCIA	243(90.3)	251(91.6)	0.305
Postoperative opioid dosage, intravenous morphine equivalents, median (IQR), mg	110.0(90.0–110.0)	110.0(90.0–110.0)	0.234

**Abbreviations:** BMI, body mass index; IQR, interquartile range; PCIA, patient controlled intravenous analgesia; TEAS, transcutaneous electrical acupoint stimulation.

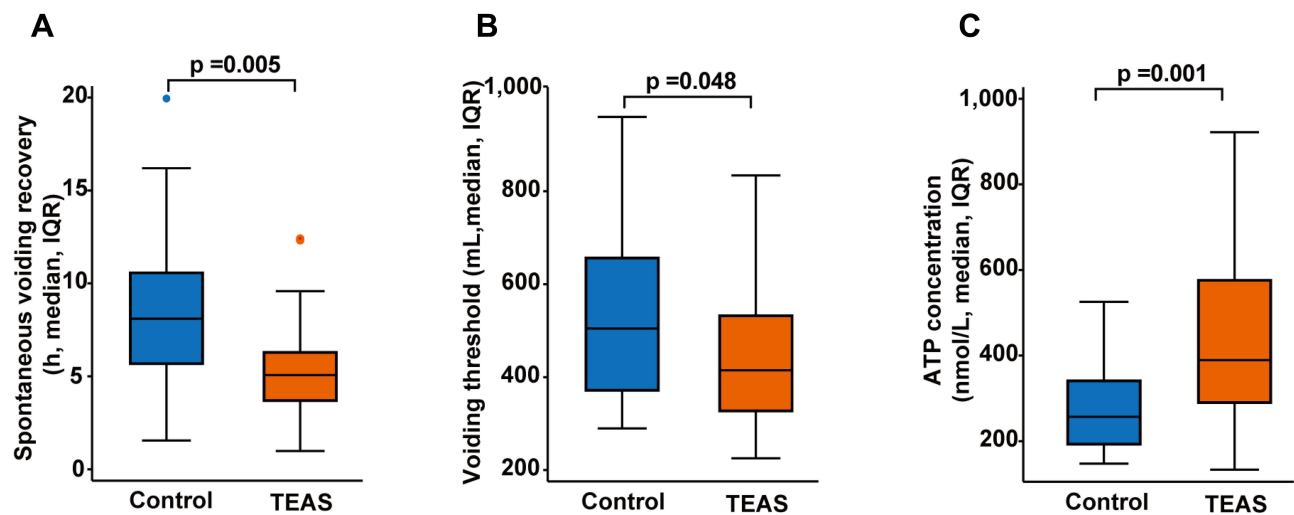
**Table 2** Postoperative Voiding and Recovery Indicators

Outcomes	TEAS Group (n=273)	Control Group (n=274)	p-value
POUR	23(8.4)	41(15.0)	0.017
Voiding difficulty	61(22.3)	129(47.1)	<0.001
Oliguria	6(2.2)	6(2.2)	0.995
Nocturia	62(22.7)	98(35.8)	0.001
Catheterization rate	23(8.4)	41(15.0)	0.017
CRBD <sup>a</sup>	3(1.1)	11(4.0)	0.031
Mild	2(0.7)	3(1.1)	0.656
Moderate	1(0.4)	4(1.5)	0.179
Severe	0	4(1.5)	0.045
Agitation	5(1.8)	14(5.1)	0.036
Delirium	1(0.4)	3(1.1)	0.317
Vomiting	72(26.4)	69(25.2)	0.750
NRS pain score, median (IQR)	5(4–6)	5(4–6)	0.104
Mobilization within 24 hours after surgery	165(60.4)	145(49.3)	0.009
Hospitalization duration, median (IQR), d	8(7–11)	9(6.8–12)	0.129
Hospitalization cost, median (IQR), yuan	23,981.1(20,644.1–30,114.3)	25,904.1(21,679.4–34,155)	0.008

**Notes:** <sup>a</sup>CRBD: mild = reported only upon direct inquiry, moderate = spontaneous complaints by the patient without behavioral responses (eg, pulling out the catheter, flailing limbs, or a loud vocal response), and severe = spontaneous complaints by the patient with behavioral response.

**Abbreviations:** CRBD, catheter-related bladder discomfort; IQR, interquartile range; NRS, numerical rating scale; POUR, postoperative urinary retention; TEAS, transcutaneous electrical acupoint stimulation.





**Figure 3** Postoperative spontaneous voiding recovery and urinary ATP. (A) spontaneous voiding recovery, (B) Voiding threshold, (C) ATP concentrations (n=30 in the TEAS group; n=30 in the control group).

elderly, and catheter-associated urinary tract infections are more prevalent among the needy.<sup>22</sup> In the present study, a significant reduction in the incidence of POUR after TEAS treatment was observed as compared to the baseline incidence of 15% in the elderly, which was consistent with previous research. Furthermore, no urinary tract infections occurred in patients treated with TEAS, indicating that TEAS has a protective effect on urinary tract susceptibility in older adults.

The storage and elimination of urine are essential aspects of daily life and involve intricate neural signaling pathways that require coordination between the urinary bladder and the urethra.<sup>23</sup> It is necessary for both continence and micturition that the autonomic nerves and somatic nerves cooperate to control the bladder and urethra. During the storage phase of the micturition cycle, the sympathetic nervous system inhibits the contraction of the smooth muscle in the detrusor. As a result, the bladder is able to relax and expand. As the urinary bladder empties, ATP and acetylcholine act on smooth muscle P2X purinoceptor 1 (P2X1) and muscarinic receptors (M2 and M3) to mediate contractions. A switch from the filling phase to the emptying phase occurs when tension in the bladder stimulates stretch receptors (which are slowly adapting mechanoreceptors).<sup>24</sup> Inhibition of the parasympathetic nerves that innervate the bladder is the mechanism by which anticholinergics, opioids, and anesthetics cause urinary retention.<sup>25,26</sup> There are numerous signaling molecules secreted by the urinary epithelium (including acetylcholine, nitric oxide, neuropeptides, neurotrophins, and prostaglandins) which form the “uroepithelium-associated sensory network”, with ATP serving as the main messenger for the voiding reflex and pain.<sup>27</sup> In experiments, administration of intravesical ATP increased afferent firing induced by bladder distension, decreased the voltage threshold for electrical stimulation, and increased the area of action potentials.<sup>28</sup> In rats with bladder dysfunction caused by AUR, ATP-sensitive potassium channel openers prevent the need

**Table 3** Adverse Events

Outcomes	TEAS Group (n=273)	Control Group (n=274)	P-value
Voiding-related adverse events			
Gross hematuria	2(0.7)	1(0.4)	0.560
Lower urinary tract infections	0	1(0.4)	0.157
Treatment-related adverse events			
Redness	1(0.4)	1(0.4)	0.998
Itching	1(0.4)	0	0.318

for catheterizations as a result of the dysfunctional bladder.<sup>29</sup> The present study found elevated urinary ATP levels in TEAS of laparoscopic cholecystectomy patients, which may be associated with lower urinary retention rates.

An elderly person's ability to adapt to environmental or intrinsic visceral stimuli is compromised due to significant changes in autonomic nervous system function as they age. There is evidence that the elderly has altered peripheral and central nervous system activity, as well as reduced neurotransmitter receptor function. As a result, bladder capacity is reduced and bladder volume sensation is lost.<sup>30</sup> In order to increase sympathetic, parasympathetic, and central cholinergic activity, simple strategies can be implemented to enhance autonomic function and increase cortical blood flow. By inhibiting ATP release from the urothelium and attenuating bladder afferent nerve firing, OnabotulinumtoxinA is able to exert its clinical effects on urinary urgency in cases of overactive bladder syndrome.<sup>31</sup> Alternatively, acupuncture-like stimulation of specific body areas causes an increase in bladder tone and a decrease in periurethral electromyogram activity when the bladder is full and contracting.<sup>32</sup> This response is mediated through the pelvic efferent (parasympathetic) nerve that drives the bladder and depends on the state of the bladder's filling.<sup>33</sup> Adenosine A1 receptors and local anti-nociceptive effects of acupuncture have been shown in research to increase ATP concentration in the body, as well as adenosine levels.<sup>34</sup> As a result of the present study, patients receiving TEAS treatment had higher urinary ATP levels and significantly faster recovery from voluntary voiding after surgery. Thus, increasing urinary ATP levels are related to the regulation of TEAS during urination.

This study has several limitations. First, we evaluated only the incidence of urinary retention following laparoscopic cholecystectomy and short-term after catheter removal, without long-term follow-up of voiding relief and functional outcomes. Second, despite the careful blinding procedure, there may be a potential placebo effect. Third, this study demonstrated that people with elevated ATP concentrations had a reduced bladder voiding threshold, although the specific mechanism remains to be determined.

## Conclusion

TEAS can reduce the incidence of POUR and increase ATP release in elderly patients who have undergone laparoscopic cholecystectomy. Future studies should examine specific mechanisms by which ATP participates in TEAS to reduce bladder dysfunction caused by urinary retention.

## Data Sharing Statement

The datasets generated during and/or analyzed during the current study will be available upon reasonable request from the corresponding author. Email: 30717008@nankai.edu.cn.

## Ethical Approval

The study was approved by Tianjin Nankai Hospital Ethics Committee (ethical register number: NKYY\_YX\_IRB\_2017\_032\_01). Trial Registration: NCT03631160.

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.



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