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Transcutaneous electric acupoint stimulation reduces rocuronium injection-related pain: a prospective randomized controlled study

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Abstract. – OBJECTIVE: Various approaches have been suggested to reduce the pain and discomfort associated with rocuronium injection. This randomized controlled trial aimed at exploring the effectiveness of transcutaneous electrical acupoint stimulation (TEAS), a non-invasive modality to reduce the pain associated with rocuronium injection.

PATIENTS AND METHODS: 60 patients undergoing elective general anesthesia were recruited and randomly allocated to the TEAS or placebo TEAS (no electrical output) groups. TEAS consisted of 30 min of stimulation at a frequency of 2/100 Hz and an intensity of 6-9 mA on Hegu (LI4) and Neiguan (PC6) before anesthesia induction. A blinded observer evaluated the pain using a 4-point pain scale.

RESULTS: The overall incidence of rocuronium injection-related pain was significantly lower in the TEAS group than that in the placebo TEAS group (40% and 86.7%, respectively). The incidence of no or mild pain was significantly higher in the TEAS group (100%, p<0,001) group than that in the placebo TEAS group (50%).

CONCLUSIONS: Pretreatment with TEAS effectively reduced the frequency and severity of pain associated with rocuronium injection.

Key Words:
Transcutaneous electrical acupoint stimulation, Rocuronium, Pain.

Abbreviations

ASA: American Society of Anesthesiologists; D-D: Dense-and-disperse; ECG: Electrocardiography; NO: Nitric oxide; SpO_2: Oxygen saturation; TEAS: Transcutaneous electrical acupoint stimulation; TENS: Transcutaneous electrical nerve stimulation.

Introduction

Rocuronium is a non-depolarizing muscle relaxant with rapid onset and moderate duration of action; hence, it is preferred for the induction of general anesthesia. Unfortunately, pain after intravenous rocuronium injection is widespread in the clinical setting, with an incidence ranging from 50% to 80%[1,2]. In addition, the pain associated with the injection may result in a withdrawal movement of the arm even in unconscious patients who are administered anesthetic induction agents, which may increase the risk of venous catheter displacement and difficulties of intravenous drug injection[3,4]. Furthermore, excessive movements during induction may induce injury, and pulmonary aspiration due to gastric regurgitation has been documented in children[5]. Due to the unique position of rocuronium among non-depolarizing relaxants. Various pharmacologic and non-pharmacologic approaches have been suggested to reduce the incidence and severity of pain associated with rocuronium bromide injection[6].

Acupuncture is a traditional Chinese medicinal technique that involves inserting needles into acupuncture points to treat acute and chronic pain, and it is recommended as part of a balanced anesthetic technique[7-9]. However, acupuncture is invasive, and its application requires a physician experienced in this technique. Transcutaneous electrical acupoint stimulation (TEAS) is a non-invasive treatment that combines acupuncture and transcutaneous electrical nerve stimulation (TENS) and acts on the corresponding acupoints through low frequency pulsed electrical stimulation[10]. It has no risk of infections and can be used by medical personnel with minimal training. Clinical trials have revealed that TEAS decreases the consumption of intraoperative anesthetics and general anesthesia-related side effects[11-13]. However, the effect of TEAS on preventing rocuronium injection-related pain is unknown. Therefore, this randomized, double-blind

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study was designed to evaluate the effectiveness of TEAS pretreatment in reducing the pain associated with the administration of rocuronium.

Patients and Methods

This prospective randomized controlled study was conducted at the Konya City Hospital in accordance with the principles of the Declaration of Helsinki after receiving ethical approval from the University of Health Sciences Faculty of Medicine Ethics Committee (no. 2020-008, dated 12/31/2020). The trial was registered prior to patient enrollment at clinicaltrials.gov (Reg. NCT04943367, principal investigator: Betul Kozanhan, date of registration: 06/18/2021). Written informed consent was obtained from all patients. A CONSORT checklist was used to enroll and allocate the patients (Figure 1).

Between October 2021 and December 2021, patients aged 18-65 years, American Society of Anesthesiologists (ASA) grade I–III, and volunteers scheduled for elective surgery under general anesthesia were included in the study. Patients who had renal, hepatic, cardiac, neurological, or any known psychiatric disease, had undergone cardiac and cranial surgery, had a pacemaker, required rapid serial induction, and in whom could not establish venous access from the back of the hand were excluded from the study.

The patients were assigned to the placebo TEAS group with no electrical output (Group P) and the TEAS group (Group T), using the closed-envelope method. The acupuncturist was informed about the randomization allocation immediately prior to the initiation of the TEAS. None of the participants or anesthesiologists who administered the rocuronium injection were aware of the allocation. Additionally, the patients in Group P were blinded to the allocation by sticking gel pads to the acupuncture points.

According to traditional Chinese medicine theory, bilateral Hegu-LI4 and Neiguan-PC6 were chosen as acupuncture points[14]. Gel electrodes were applied to the skin after cleaning with ethyl alcohol. An experienced acupuncturist administered TEAS using Han's acupoint nerve stimulator (LH202H, Beijing Huawei Co., Ltd., Beijing,

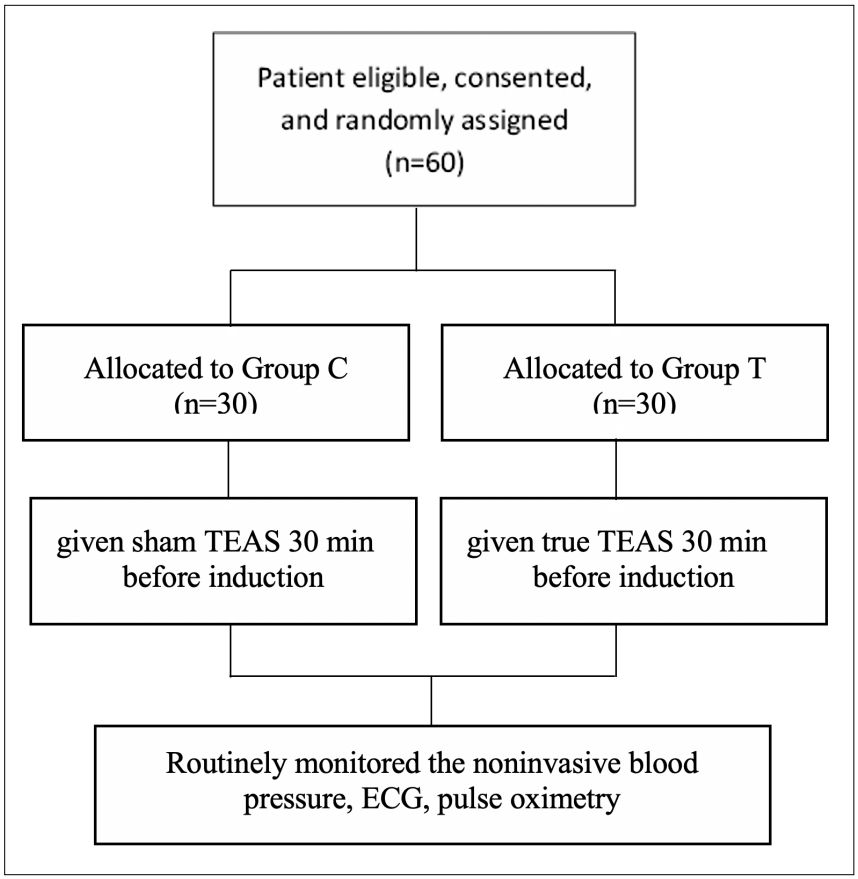

Figure 1. Flow chart showing study procedures and the number of patients. TEAS; transcutaneous electrical acupoint stimulation.

China) for 30 minutes before the induction of general anesthesia. Stimulation was performed in the standard dense-and-disperse (D-D) mode at a frequency of 2/100 Hz and an intensity of 6-9 mA. The optimal intensity depended on the ability of the patient to tolerate the stimulation. In the placebo TEAS group, the gel electrodes were applied at the same anatomical points TEAS' device without stimulation. The patients were informed that they may or may not experience a tingling sensation near the electrode area when the TEAS device worked.

The patients were taken to the operating room without premedication. Intravenous access was attained with a 20-gauge (G) granule on the dorsum of the non-dominant hand, and ringer lactate infusion was initiated at 5 mL · kg^{-1} · h^{-1}. All patients underwent the standard anesthesia protocol following routine monitoring of electrocardiography (ECG), peripheral oxygen saturation (SpO2), and non-invasive blood pressure measurement. Following the pre-oxygenation of the lungs with 100% oxygen for 3 min through face mask ventilation, rocuronium (0.06 mg/kg) was administered within 10 seconds. Anesthesia was induced with 5 mg · kg^{-1} pentothal (iv), 0.54 mg · kg^{-1} rocuronium (iv), and 1 μg · kg^{-1} fentanyl (iv) 30 seconds after priming. An anesthesiologist, who was unaware of the allocation, checked the injection site for pain, edema, or allergic reaction within 24 hours of surgery.

The sex, age, height, and weight of the patients were evaluated. The assessment of the severity of rocuronium injection-related pain was performed by a researcher who was blinded to the group distribution of the patients, using the 4-point pain scale (Table I) developed by McCrirrick[15].

Sample Size

Rocuronium injection-related pain was observed in 80% of the patients[16]. A power analysis was performed to determine the minimum number of participants required to establish that pretreatment TEAS could produce a 50% decrease in rocuronium-related pain, assuming a significance level of 0.05, one-sided, and a power of 95% using G power software's two independent proportions (n=30 per group).

Statistical Analysis

All statistical analyses were performed using the Statistical Package for the Social Sciences version 22 software (SPSS, IBM Corp., Armonk, NY, USA). The normal distribution of the data was checked using the Shapiro-Wilk test. Numerical variables were compared using the independent-samples *t*-test and are presented as the mean ± standard deviation. Categorical variables were compared using the Chi-square and Fisher's exact tests and presented as numbers (n) and percentages (%). Statistical significance was set at $p<0.05$.

Results

82 patients were assessed for eligibility: 22 patients were excluded, 20 did not meet the inclusion criteria, and 2 refused to participate. 30 patients underwent TEAS treatment after randomization, and 60 patients completed the study (Figure 1). There were no significant differences in sex, age, height, or weight between the two groups (Table II). The grade and incidence of rocuronium injection-related pain responses in each group are shown in Table III.

The overall incidence of rocuronium injection-related pain was significantly lower in the TEAS group than that in the Group P (40% and 86.7%, respectively). The incidence of no or mild pain was significantly higher in the Group T (100%, $p<0.001$) than that in the Group P (no electrical output, 50%). In addition, no patients receiving TEAS had severe pain, which was significantly higher in the Group P (no electrical output) than that in the Group T ($p<0.001$). There were no complications such as wheals, inflammation, or allergic reactions at the injection site 24 h postoperatively.

Table I. Assessment of pain.

Pain score	Degree of pain	Response
0	None	Negative response to questioning.
1	Mild	Pain reported in response to questioning only without any behavioral signs.
2	Moderate	Pain reported in response to questioning and accompanied by a behavioral sign or pain reported spontaneously without questioning.
3	Severe	Strong vocal response or response accompanied by facial grimacing, arm withdrawal, or tears.

Table II. Patient characteristics in groups.

	Group T (n = 30)	Group P (n = 30)	*p*-value
Age, years	36 ± 14	40 ± 13	0.805
Weight, kg	75 ± 14	76 ± 12	0.713
Height, cm	168 ± 10	168 ± 9	0.068
Gender, M/F (n, %)	12/18 (40/60%)	13/17 (43/57%)	0.793
ASA I/II/III, n	12/17/1	8/21/1	0.543

Discussion

This prospective randomized study demonstrated that TEAS pretreatment at LI4 and PC6 30 minutes before surgery significantly reduced the incidence and severity of pain associated with rocuronium injection. To the best of our knowledge, this is the first randomized controlled trial to examine the effectiveness of TEAS in preventing the pain related to rocuronium injection.

In the absence of preventive action, the incidence of rocuronium injection-related pain has been reported as approximately 50-80%[1,2]. Since rocuronium is unique among non-depolarizing relaxants, continuous efforts have been made to alleviate this painful side effect, and various pharmacological interventions have been proposed. Adding sodium bicarbonate prior to administration or in combination with other drugs, such as oxycodone, lidocaine, esmolol, and alfentanil, may successfully reduce the pain induced by rocuronium. However, these pharmacological interventions can require additional effort or add complexity by requiring the preparation of an additional drug and trigger adverse events, such as opioid-induced breath-holding and stiffness[6,17,18]. Therefore, these interventions have not been widely accepted yet.

Non-pharmacological methods such as massaging, rubbing, warming the injection site, and diluting with rocuronium with saline have also been used to reduce the pain associated with rocuronium injection. However, there is uncertainty regarding the mean reduction in pain due to the low quality of evidence[6]. Zhang et al[19] reported a significant reduction in the incidence and severity of pain associated with rocuronium injection using a large vein. However, the use of the antecubital fossa is generally not recommended in clinical anesthesia practice. Instead, it is chosen when the veins in the wrist and dorsum of the hand are unsuitable for catheterization. In our study, the rate of rocuronium injection-related pain was 86.7% in the Group P, in line with previous findings. However, we found that the use of TEAS resulted in a decrease of over 50% in the pain associated with rocuronium injection.

TEAS produces anti-inflammatory and analgesic effects similar to those of acupuncture or electroacupuncture therapy *via* a particular low-frequency pulse current into the body through the skin. The mechanism underlying the analgesic effect of TEAS is not precise; however, increasing blood flow and vasodilation in several regions is a well-known systemic effect of acupuncture. Recently authors reported that abolishing nitric oxide (NO) production and improving prostaglandin E2 synthesis might be held by rocuronium injection-related pain or withdrawal movement[20]. NO is a potent vasodilator that regulates vascular tone and potentially exerts a vasoprotective effect in the vascular wall[21,22]. Acupuncture treatment increases the level of NO in treated areas and increases local circulation, clearing the region of exacerbating metabolites and chemical mediators[23]. In addition, electroacupuncture prevents pain by activating bioactive chemicals such as β-endorphin, met-enkephalin, corticotropin-re-

Table III. Incidence and grades of rocuronium injection-related pain responses.

Group	Grade of pain response				Overall incidence
	0: No pain	1: Mild pain	2: Moderate pain	3: Severe pain	
Group T (n, %)	18 (60%)	12 (40%)	0 (0%)	0 (0%)	12 (40%)
Group P (n, %)	4 (13.3%)	11 (36.7%)	11 (36.7%)	4 (13.3%)	26 (86.7%)

Values are presented as numbers of patients (percentages).

leasing factor, and prostaglandin E2 via peripheral, spinal, and supraspinal mechanisms[24,25]. These regulatory effects might contribute to a reduction in pain associated with rocuronium injection provided by TEAS.

Limitations

In the present study, 60% of the patients did not experience pain after TEAS; however, 40% experienced mild pain. The intensity of pain decreased, and most patients experienced only mild pain. Therefore, TEAS administration is a cost-effective and safe method for reducing the pain associated with rocuronium injection. However, this study has some limitations, including limited sample size. In addition, we chose to evaluate only the severity of pain associated with rocuronium injection, as the primary outcome in patients and did not investigate the biochemical factors in our study. Lastly, different combinations of drugs and methods were not used to examine the efficacy of TEAS in reducing the incidence and severity of pain associated with rocuronium injection. Further studies using pharmacologic and non-pharmacologic interventions with TEAS are required to determine the best combination for reducing the pain associated with rocuronium injection.

Conclusions

Preventing pain associated with rocuronium injection using TEAS is an effective, safe, and simple technique.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

This prospective randomized controlled study was conducted at the Konya City Hospital in accordance with the principles of the Declaration of Helsinki after receiving ethical approval from the University of Health Sciences Faculty of Medicine Ethics Committee (no. 2020-008 dated 12/31/2020).

Informed Consent

Written informed consent was obtained from all patients.

Clinical Trial Number

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Authors' Contribution

Munise Yildiz: this author helped conceptualize and design the study and data collection instruments; acquire, analyze, and interpret the data; draft the initial manuscript; and review and approve the final manuscript. Betul Kozanhan: this author helped conceptualize and design the study and data collection instruments; acquire, analyze, and interpret the data; draft the initial manuscript; and review and approve the final manuscript.

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