Efficacy of a Transdermal Nicotine Patch in Pain Relief after Arthroscopic Shoulder Surgery: A Randomized Controlled Trial

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Background: *Perioperative nicotine administration was suggested to reduce pain scores and opioid consumption in visceral pain control. However, there is no evidence to support the analgesic effect of nicotine administration in postoperative somatic pain.*

Objective: *To study the efficacy of transdermal nicotine patches (TNP) in postoperative somatic pain relief by assessing numerical rating scale (NRS) scores and opioid consumption.*

Material and Method: *A prospective, double-blind, placebo-controlled study was conducted in 46 patients, who received general anesthesia for elective arthroscopic shoulder surgery. All participants were randomly allocated to receive a patch of 7 mg nicotine or placebo before induction of anesthesia and remaining for 24 hours after surgery. Participants and assessors were blinded to allocation. Average pain score and intravenous morphine patient-controlled analgesia (PCA) consumption were assessed at 1 hour and 24 hours postoperatively.*

Results: *There was no significant difference in mean NRS and average opioid consumption at 1 hour and 24 hours postoperatively between controlled and treatment group. However, the significant reduction in average NRS from baseline at 1 hour and 24 hours postoperatively were found in both groups ($p<0.001$).*

Conclusion: *Administration of a 7 mg TNP did not significantly reduce in pain scores and postoperative opioid consumption compared with transdermal placebo during perioperative elective arthroscopic shoulder surgery.*

Keywords: *Transdermal nicotine patch, Postoperative pain control, Multimodal analgesia, Arthroscopic shoulder surgery*

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Postoperative pain appears to be significant factor affecting rapid recovery following surgery in many patients[1]. Systemic opioid analgesic remains a cornerstone of pain management with the risk of respiratory depression and prolonged time spent in hospital[2]. To reduce the dose requirements and side effects, opioids should be used in an effort to achieve multimodal analgesia and more optimal pain management[3].

The primary psychoactive component of cigarette smoke "nicotine" was found to have anti-nociceptive effects in animal models and human studies[4,5]. Anti-nociceptive effects of nicotine was reported to involve the activation of descending inhibitory pain pathway via central[6-8] and peripheral action[9]. A systematic review and meta-analysis of nicotine for postoperative analgesia suggests that perioperative nicotine administration was associated with a reduction in cumulative opioid consumption but no reduction in 24-hour postoperative pain scores[10]. All nine studies included in the systematic review[10] were conducted in visceral pain operation, such as pelvic and abdominal surgery, which associated with silent nociceptors and autonomic nervous system. Although nicotine is widely acknowledged to possess visceral analgesic properties, there is surprisingly no clinical study in the literature evaluating its analgesic effect on somatic pain.

In the present randomized, double blind, placebo-controlled study; we hypothesized that the perioperative application of a transdermal nicotine patch or TNP added to intravenous morphine patient-controlled analgesia (PCA) would decrease postoperative arthroscopic shoulder surgery pain and opioid analgesic usage, thereby improving the early recovery process after arthroscopic shoulder surgery.

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Material and Method

After the Institutional Review Board of the Royal Thai Army Medical Ethics Committee approved

the present study (ref. number R 184h/57 Date: 18-February-2015), which was conducted at Phramongkutklao Hospital between February and September 2015. All patients gave informed consents. Eligible patients were adults aged 18 to 70 years, with American Society of Anesthesiologists (ASA) physical status I-II undergoing elective arthroscopic shoulder surgery and could operate a PCA device. Patients who have history of allergic reaction to any of the study medications, contraindications to the use of the PCA morphine or any anesthetic drugs, chronic pain syndromes, a history of uncontrolled hypertension, myocardial disease, stroke, respiratory disease, psychological problems, language barriers, pregnancy and the use of brachial plexus block during the operation were excluded.

All patients were prospectively assigned to one of two treatment groups using a computer-generated randomization table. The control group obtained inert (placebo) patches, and the nicotine group obtained 10 TNP containing 17.5 mg of nicotine, with the release of 7 mg of nicotine in 24 hours (Novartis, Nyon, Switzerland). All patches were identical in appearance, and were placed on the patient's abdomen and covered with a sterile gauze and taped by nurse anesthetists who not involved in the data collection process. The patches were applied immediately after induction of anesthesia and removed at 24 hours postoperative period. The patients, investigators, and assessors were blinded.

Anesthesia was induced with propofol (2 mg/kg IV) and atracurium (0.5 mg/kg IV), and maintained with sevoflurane, 1.5 to 2% inspired, at a fresh gas flow rate of 2 L/minute in combination with nitrous oxide 50% in oxygen. Fentanyl 2 mcg/kg IV, was administered three to five minutes before the surgical incision. Surgery was performed under arthroscopic technique of shoulder. Patients' lungs were mechanically ventilated to maintain an end-expiratory CO_2 value between 35 and 40 mmHg. All patients received Ondansetron 8 mg for postoperative nausea and vomiting (PONV) prophylaxis within 30 minutes of the end of surgery. Fentanyl was titrated intraoperatively depends on anesthesiologist staffs adjustment. Neuromuscular blockade was reversed with neostigmine (2 to 3 mg, IV), and atropine (0.3 to 0.6 mg, IV). PCA was administered at Post Anesthesia Care Unit (PACU) after tracheal extubation, which was composed of intravenous morphine at 1 mg bolus dose, no basal rate, 5-minute lockout, and 4 hours limit of 30 mg. Sedation score was recorded (0 = no sleepiness or drowsiness and 2 = almost asleep and/or extremely drowsy). No additional analgesics were allowed since induction through 24 hours postoperatively.

A blinded assessor evaluated all participants using numerical rating scale (NRS) scores and intravenous PCA morphine consumption in the recovery room at the first hour and 24th hour postoperatively. Comparison of the average NRS and morphine consumption between groups was evaluated.

Statistical analysis

The sample size was estimated based on control values of the previous study[14]. Olson et al (2009)[14] indicated an average NRS score of 6.4±1.4 at 1 hour after surgery. At least twenty patients per group were required to achieve this study. Statistical analysis was performed using STATA/MP 13. Comparison of patient baseline characteristics of the study with the control group was tested by paired t-test for continuous data and Chi-square test or Fisher's exact test for categorical data. The mean visual analogue scale (VAS) was tested using paired t-test for intra-group comparison. Unpaired t-test was used to compare mean NRS scores and average morphine consumption between group. All participants were performed using an intention-to-treat analysis. A *p*-value of less than 0.05 was considered to be statistically significant.

Results

Forty-six patients were enrolled in the study. Two patients were excluded due to extended operation from arthroscopic to open shoulder surgery. There were 21 patients in the control group (C-group) and 23 patients in the nicotine group (N-group) (Fig. 1). There was no statistical difference between groups comparison in demographic data, duration of surgery, and intraoperative fentanyl utilization ($p<0.001$) (Table 1).

Significance reduction in average pain scores from baseline at 1 hour and 24 hours postoperatively was found in both groups ($p<0.001$) (Table 2, Fig. 2). However, patients treated with nicotine reported no statistical significance reduction in average pain scores when compared with those treated with placebo during the first hour and 24 hours after surgery ($p = 0.795$, 0.611, respectively) (Table 3, Fig. 3).

For morphine consumption, there was no significant difference at the first hour and the twenty-fourth hour postoperatively (Table 4).

Data collection about side effects of TNP were not recorded. However, there was no significant side effects reported while using TNP.

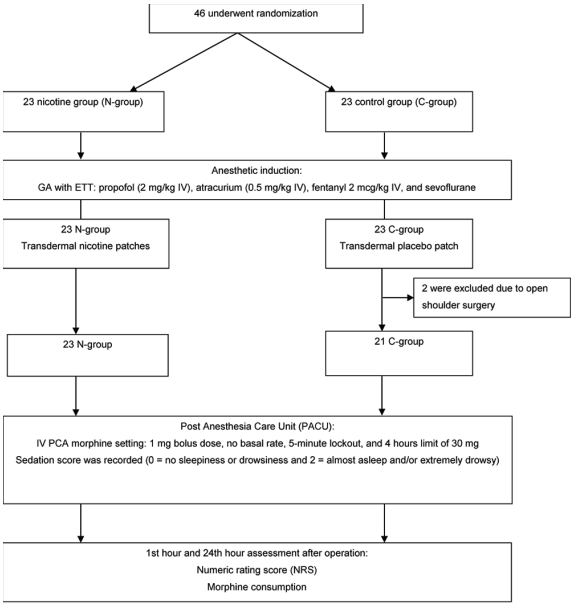

Fig. 1 Enrollment, randomization, and treatment.

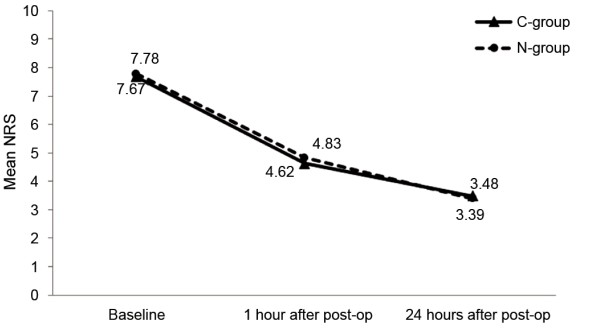

Fig. 2 Mean NRS from baseline at 1 hour and 24 hours postoperatively.

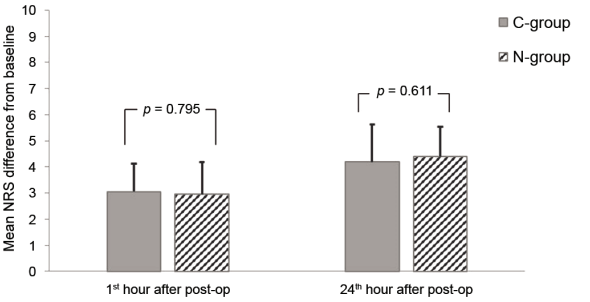

Fig. 3 Mean NRS difference from baseline between group comparison.

Table 1. Patient demographic data, intraoperative fentanyl, and duration of surgery

	C-group (n = 21), mean ± SD or n (%)	N-group (n = 23), mean ± SD or n (%)	*p*-value
Age (years)	43.86±15.73	45.43±12.98	0.718
Weight (kg)	67.76±9.45	67.70±9.86	0.982
Height (cm)	165.43±7.55	167.70±8.49	0.357
BMI (kg/cm^2)	24.68±2.34	24.07±3.08	0.464
Gender			0.783
Male	11 (52.4)	13 (56.5)	
Female	10 (47.6)	10 (43.5)	
Underlying			0.490
No	14 (66.7)	13 (56.5)	
Yes	7 (33.3)	10 (43.5)	
Cigarettes (packed year)	9.38±4.41	10.14±3.44	0.716
Duration of surgery (hour)	4.15±0.72	4.34±0.91	0.451
Intra-op Fentanyl (mcg)	345.24±78.51	354.35±82.45	0.710

BMI = body mass index

Table 2. Average NRS from baseline at 1 hour and 24 hours postoperatively

	Mean NRS (baseline)	Mean NRS (1 hour after post-op)	*p*-value	Mean NRS (24 hours after post-op)	*p*-value
C-group	7.67±1.24	4.62±1.07	<0.001	3.48±0.81	<0.001
N-group	7.78±1.20	4.83±0.78	<0.001	3.39±0.72	<0.001

NRS = numerical rating scale

Table 3. Mean NRS difference from baseline between group comparison

NRS	C-group, mean ± SD	N-group, mean ± SD	*p*-value
1st hour after post-op	3.05±1.07	2.96±1.22	0.795
24th hour after post-op	4.19±1.44	4.39±1.16	0.611

Table 4. Average morphine consumption between group comparison

	C-group, mean ± SD	N-group, mean ± SD	*p*-value
At 1st hour postoperative (mg)	3.81±0.81	3.61±0.99	0.468
At 24th hour postoperative (mg)	16.76±4.39	18.22±4.72	0.297

Discussion

Previous human studies suggested that perioperative nicotine administration for postoperative visceral pain control, such as abdominal surgery and gynecologic surgery was associated with a reduction in 24 hours opioids consumption, but no reduction in pain scores 24-hour postoperatively[10]. However, current data do not evidence a role in postoperative somatic pain analgesia. Our study, included patients undergoing elective arthroscopic shoulder surgery which related to somatic pain, found that the perioperative application of TNP (7 mg) resulted in an insignificant reduction in pain scores and morphine consumption. The former result was in accordance with previous reports in meta-analysis[10] but the latter was different.

Nicotine appears to possess a variable anti-nociceptive effect in volunteer experimental previous studies[4,5], nevertheless, the exact mechanism of nicotine against pain is still unclear. The possibility proposed to explain our finding is that the nicotine may act differently in different type of pain which is somatic and visceral pain. The visceral pain related to visceral organ silent nociceptor, but somatic pain was not[11]. The variable anti-nociceptive effect was also thought to be associated with autonomic nervous system, mediated via activation of nicotinic acetylcholine receptors at ligand-gated ion channels[12]. These might explain why TNP was significant reduced opioid consumption in postoperative somatic pain, but not significant in visceral pain.

The present study had some limitations, the authors focus only arthroscopic shoulder surgery. However, more varieties of somatic pain-related operations and more patients are needed to accomplish significant result. TNP (7 mg) were used in the present study in accordance to the previous studies of TNP (5 to 15 mg), could reduce postoperative pain scores after general surgical procedures[13,14]. However, Turan et al (2008) determined that perioperative administration of a high-dose TNP (21 mg) did not improve postoperative pain control or decrease the analgesic requirement after pelvic gynecological surgery[15]. These made the adequate TNP dose for postoperative pain control remain inconclusive. Other limitations were individualized transdermal nicotine absorption, history of nicotine exposure and nicotine blood levels should be collected. Further studies regard to the physiologic study of nicotine mechanism for pain reduction and larger clinical trials to obtain more epidemiological data from various types of somatic pain related surgical operations are required to determine the nicotine action.

Conclusion

The authors' findings indicated that the perioperative TNP for postoperative somatic pain in patients undergoing elective arthroscopic shoulder surgery did not significantly reduce pain scores nor cumulative morphine consumption at the first hour and the twenty-fourth hour. However, the difference of somatic and visceral pain pathway may play an important role of nicotine patch treatment for postoperative pain control.

What is already known on this topic?

Nicotine possesses the anti-nociceptive effects in animal and volunteer studies. Previous human studies summarized that the perioperative nicotine administration was related to a reduction in cumulative opioid consumption but not in 24-hour postoperative pain scores reduction. Previous studies focused on visceral pain operation which silent nociceptors and autonomic nervous system play important roles[10].

What this study adds?

Our study is the first randomized controlled trial of TNP efficacy for postoperative pain relief

conducted in somatic pain related operation, which is arthroscopic shoulder surgery. The perioperative application of a 7 mg TNP in patients underwent elective arthroscopic shoulder surgery was a statistically insignificant reduction in pain scores and cumulative morphine consumption at the first hour and the twenty-fourth hour.

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Potential conflicts of interest

None.

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การศึกษาประสิทธิภาพของการใช้นิโคตินชนิดแผ่นแปะผิวหนัง: ขณะผ่าตัดเพื่อลดอาการปวดหลังผ่าตัดส่องกล้องหัวไหล่

วรรณวิภา มาลัยทอง, สิทธาพันธ์ มั่นชูพงศ์

ภูมิหลัง: *การระงับปวดหลังผ่าตัดถือเป็นปัจจัยพื้นฐานที่ผู้ป่วยทุกรายจำเป็นต้องได้รับ ซึ่งการระงับปวดที่ดีจะช่วยลดการเกิดภาวะแทรกซ้อนที่เกี่ยวข้องกับการระงับปวดที่ไม่เพียงพอ โดยการศึกษาก่อนหน้าพบว่าการใช้นิโคตินสามารถลดอาการปวดหลังผ่าตัดได้ ซึ่งการศึกษาส่วนใหญ่นั้นทำศึกษาในผู้ป่วยที่ได้รับผ่าตัดเกี่ยวกับอวัยวะภายใน แต่ในปัจจุบันนั้นยังไม่มีการศึกษาถึงประสิทธิภาพของนิโคตินในการลดปวดหลังผ่าตัดชนิดที่ไม่เกี่ยวกับอวัยวะภายในมาก่อน*

วัตถุประสงค์: *เพื่อศึกษาประสิทธิภาพของการใช้นิโคตินชนิดแผ่นแปะผิวหนังในขณะผ่าตัดเพื่อลดอาการปวดหลังผ่าตัดชนิดเฉียบพลันในผู้ป่วยที่ได้รับการผ่าตัดส่องกล้องหัวไหล่*

วัสดุและวิธีการ: *เป็นการศึกษาโดยการทดลองแบบสุ่มและมีกลุ่มควบคุมโดยเก็บข้อมูลจากผู้เข้าร่วมการศึกษา 46 ราย อายุระหว่าง 18-65 ปี ที่ได้รับการระงับความรู้สึกทั่วร่างกาย เพื่อการผ่าตัดส่องกล้องหัวไหล่ในโรงพยาบาลพระมงกุฎเกล้า ระหว่างเดือนกุมภาพันธ์ ถึง กันยายน พ.ศ. 2558 ซึ่งผู้เข้าร่วมการศึกษาจะถูกแบ่งเป็นสองกลุ่มโดยการสุ่ม คือ กลุ่มทดลองจะเป็นกลุ่มที่ได้รับแผ่นแปะนิโคติน และกลุ่มควบคุมจะเป็นกลุ่มที่ได้แผ่นแปะหลอก โดยที่คะแนนความปวดและปริมาณยาแก้ปวดที่ผู้ป่วยต้องการจะถูกบันทึกข้อมูลที่เวลา 1 ชั่วโมง และ 24 ชั่วโมงหลังผ่าตัด ใช้การวิเคราะห์แบบ unpaired t-test เพื่อหาความแตกต่างของประสิทธิภาพ การลดปวดระหว่างกลุ่มที่ใช้นิโคตินชนิดแผ่นแปะผิวหนัง และกลุ่มควบคุม โดยถือค่า $p < 0.05$ มีนัยสำคัญทางสถิติ*

ผลการศึกษา: *ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างกลุ่มที่ได้แผ่นแปะนิโคตินและกลุ่มควบคุมทั้งระดับความปวดและปริมาณยาแก้ปวดที่ผู้ป่วยต้องการ ที่เวลา 1 ชั่วโมง และ 24 ชั่วโมงหลังผ่าตัด ในการการผ่าตัดส่องกล้องหัวไหล่*

สรุป: *การใช้แผ่นแปะนิโคตินขนาด 7 มิลลิกรัม ไม่สามารถช่วยลดคะแนนความปวดและปริมาณยาแก้ปวดที่ผู้ป่วยต้องการในเวลา 1 ชั่วโมง และ 24 ชั่วโมงหลังผ่าตัด เมื่อเทียบกับกลุ่มที่ไม่ได้ใช้แผ่นแปะนิโคตินในการผ่าตัดส่องกล้องหัวไหล่*