Transdermal nicotine patch as adjunctive analgesic modality to thoracic epidural analgesia for post-thoracotomy pain

Heba Ismail Ahmed Nagy, Hany Wafik ElKadi

Department of Anesthesia, Faculty of Medicine, Cairo University, Cairo, Egypt

Correspondence to Hany Wafik ElKadi, MD, Kasr Al Aini School of Medicine, Cairo University Hospitals, Department of Anesthesia and Surgical Intensive Care, Matehaf El Manyal Street, Cairo, Egypt
Tel: +201000966382; fax: +202 3641687;
e-mail: hanimwk@yahoo.com

Received 24 December 2013
Accepted 16 February 2014

The Egyptian Journal of Cardiothoracic Anesthesia 2014, 8:75–82

Objective
The aim of the study was to evaluate the applicability of transdermal nicotine patch (TNP) as an analgesic modality adjunctive to thoracic epidural analgesia (TEA) for patients undergoing thoracotomy.
Patients and methods
The current study included 100 adult nonsmoker male patients assigned to undergo thoracotomy and resection for lung cancer. Patients were randomly allocated into two equal groups: group N received TNP (5 mg/16 h) applied to glabrous skin immediately before induction of anesthesia and group C included patients who received placebo patch. All patients received bupivacaine (0.125%) TEA initiated at the time of induction of anesthesia until 48 h postoperative (PO). All patients received a β-lactam antibiotic as prophylactic and PO antibiotic. Rescue analgesia was provided as increments of dose of epidural bupivacaine until 48 h PO, and thereafter as intravenous meperidine 50 mg. PO pain was assessed using 10-point visual analog scale (VAS) and rescue analgesia was given if VAS was greater than 4. Intraoperative variability of heart rate and blood pressure measures, the frequency of requests for PO rescue analgesia, and the frequency of postoperative nausea and vomiting (PONV) were recorded.
Results
Epidural analgesia induced significant decrease in systolic arterial blood pressure and mean arterial blood pressure estimated at the end of surgery in both groups. Nicotine induced significantly higher heart rate compared with baseline measures in group N. Mean systolic arterial blood pressure and mean arterial blood pressure measures estimated at the end of surgery were significantly higher in group N compared with group C. Pain VAS scores were significantly lower in group N compared with group C throughout the first 48 h after admission to ICU, but thereafter pain VAS scores were significantly higher as against that determined at 48 h after ICU admission, in both groups. Pain VAS scores were significantly lower in group N compared with group C after removal of epidural catheter until 80 h after the end of surgery. The number of requests of rescue analgesia was significantly higher in group C compared with group N. TNP significantly reduced the number of requests of rescue analgesia after removal of epidural catheter in comparison with placebo. The frequency of PONV was significantly higher in group N compared with group C.
Conclusion
TNP could be considered as appropriate adjuvant analgesic to TEA for patients who had thoracotomy during early PO period and could be used as the sole analgesic after cessation of TEA. Prophylactic antiemetics were advocated to guard against the high possibility of development of PONV.

Keywords:
post-thoracotomy pain, thoracic epidural analgesia, transdermal nicotine patch

Egypt J Cardiothorac Anesth 8:75–82

1687-9090

Introduction

Pain relief is an important part of postoperative care of the patients who undergo any type of surgery. Patients deserve to be as pain free as possible. Open thoracotomy is one of the surgical procedures that is still very painful during the postoperative (PO) period. Post-thoracotomy pain is a compilation of several factors: incisional pain, pain secondary to interruption of muscular and ligamentous structures by the retractor, and pain due to pleural irritation usually secondary to chest tube [1].

In addition to patient's comfort, one of the important reasons for good pain management in patients who had thoracotomy is that the patient needs to participate fully in PO rehabilitation, such as deep breathing, coughing, and ambulation, so as to prevent unwanted complications [2,3].

Various modalities of pain control were applied either as preemptive and/or intraoperative or for PO pain control. Rabanal *et al.* [4] found that continuous thoracic paravertebral analgesia is effective and safe

in controlling post-thoracotomy pain. Momenzadeh *et al.* [5] found that cryoanalgesia is a useful technique with no serious side effects to alleviate post-thoracotomy pain and reduce the need for opiate consumption. Gupta *et al.* [6] found that thoracic epidural analgesia (TEA) is an effective analgesic modality for post-thoracotomy pain, but intravenous magnesium can prolong opioid-induced analgesia while reducing the dose of both opioid and bupivacaine and minimizing nausea, pruritus, and somnolence. Grider *et al.* [7] found that TEA with bupivacaine and a hydrophilic opioid, hydromorphone, may provide enhanced analgesia over TEA or continuous paravertebral infusion with bupivacaine alone.

Nicotine, a potent stimulant found in cigarette smoke, was found to have analgesic properties [8]. The antinociceptive effects of nicotine have been consistently observed in animal studies that also tried to explore the underlying mechanisms for such action; Rowley *et al.* [9] suggested that nicotine reduced nociceptive input to the superficial and deep dorsal horn and provides support for α4β2 and α7 nicotinic-mediated antinociceptive actions. In addition, Costa *et al.* [10] found a potential relevance of using α7 nicotinic acetylcholine receptor agonists to treat referred pain and discomfort associated with inflammatory bowel diseases.

Transdermal therapeutic systems gain continuously increasing importance in therapy because of their advantageous properties. They assure constant concentration of the active substance in the blood; a lower amount of the drug compared with the orally administered dose is sufficient; side effects decrease, and the therapy is painless. The management of transdermal therapeutics in perioperative care can be adapted for each treatment and for each patient by knowing the pharmacokinetics as well as anesthetics and surgical interactions [11–13].

The current prospective comparative study aimed to evaluate the applicability of transdermal nicotine patch (TNP) as an analgesic modality adjunctive to TEA for patients undergoing thoracotomy.

Patients and methods

The current study was conducted at the Anesthesia Department, Kasr Al-Aini University Hospital from June 2010 to January 2013. After approval of the study protocol by the local ethical committee and obtaining written fully informed patients' consent, 100 adult nonsmoker male patients assigned to undergo thoracotomy and resection for lung cancer were enrolled in the study. Patients with cardiac, renal, or hepatic diseases or sensitivity to used drugs were not enrolled in the study.

Anesthetic procedure was standardized for all patients including the use of double-lumen endobronchial tubes under fiberoptic control to allow single-lung ventilation. All patients were taken into the operating room unpremedicated and after standard monitoring with invasive blood pressure, ECG, and peripheral oxygen saturation (SpO_2); administration of lactated Ringer's solution was initiated. Patients were positioned in the lateral decubitus and after identification of the epidural space using the loss of resistance technique, a 20-G epidural catheter (Perifix 401; B. Braun Melsungen AG, Melsungen, Germany) was inserted through an 18-G Tuohy needle that was placed at the $T_{9–10}$ interspace and advanced 3–5 cm into the epidural space. After injection of 3 ml of 2% lidocaine through the epidural catheter as a test dose, negative test obtained, the catheter was fixed and the patient was repositioned supine. Continuous epidural infusion of bupivacaine 0.25% solution at 5 ml/h was initiated at the time of induction of anesthesia before skin incision to act as preemptive analgesia and was continued as intraoperative analgesia. PO infusion continued for analgesia for 48 h after surgery. The PO infusion rate was 5 ml/h of 0.125% bupivacaine solution.

General anesthesia was induced with propofol 2 mg/kg, fentanyl 2 μg/kg, and cisatracurium 0.1–0.15 mg/kg and maintained with isoflurane, fentanyl, and cisatracurium adapted to the patient's physiological reaction to surgical stimuli. After intubation of the trachea, the lungs were ventilated with 50% O_2 in air using a semiclosed circle system. Ventilation was controlled with a tidal volume of 5 ml/kg, and the ventilatory rate was adjusted to maintain an arterial partial pressure of carbon dioxide ($PaCO_2$) of 32–42 mmHg and arterial pH between 7.35 and 7.45. During the perioperative and PO period, standard monitoring included respiratory rate, SpO_2, heart rate (HR), and systolic arterial blood pressure (SAP). Hypotension, defined as a reduction in the systolic blood pressure greater than 20%, was treated with the rapid infusion of lactated Ringer's solution and intravenous boluses of ephedrine. To avoid hypothermia during the operative period, patients received prewarmed fluids. All patients received a β-lactam antibiotic (ceftriaxone) at a dose of 20 mg/kg body weight as antibiotic prophylaxis after induction of anesthesia and was continued postoperatively to guard against development of infection.

Patients were randomly, using sealed envelopes, allocated into two equal groups (n = 50). Group N

included patients who received transdermal nicotine through transdermal patches (Nicotrol 10 cm^2, containing 5 mg/16 h; manufacturer of Nicotrol Pharmacia Pfizer, Auckland, New Zealand) applied to glabrous skin away from the surgery site, immediately before induction of anesthesia. The patches were changed every 16 h until the end of observation period for 80 h PO. Group C included patients who received placebo in the form of a placebo patch applied to the same site as in group N and the patches were changed every 16 h. After removal of epidural catheter at 48 h PO, rescue analgesia provided in the form of intravenous meperidine 50 mg to be repeated according to the need and times of requests of rescue analgesia was recorded.

The primary outcome of the study included assessment of PO pain using VAS (a 10 mm scale, with '0' indicating no pain and '10' indicating worst pain ever) [14]. Pain VAS scores were determined every 6 h for 48 h until removal of the epidural catheter, and thereafter every 8 h for completion of 80 h after application of the first patch; timing of VAS determination was adjusted with the duration of action of the patch (16 h) so as to use five patches. When pain VAS was at least 4, the epidural infusion rate was increased. The secondary outcome included intraoperative variability of HR and blood pressure measures and the frequency of the requests for PO rescue analgesia and the frequency of postoperative nausea and vomiting (PONV). Granisetron, 1 mg diluted to 15 ml with normal saline, was injected intravenously over 60 s for management of PONV.

Statistical analysis

Sample power was calculated according to Kraemer and Theimann [15] using the proposed figure showing that the sample size for 60% power would require an *N* of more than 30/group and for 80% power would require an *N* of 50/group. Thus, the current study sample size was chosen to be 50 patients per group to reach a point of significance of less than 0.05. Obtained data were presented as mean ± SD, ranges, numbers, and ratios. Results were analyzed using the Wilcoxon ranked test for unrelated data (*Z*-test) and the χ^2-test. For intergroup comparisons, paired *t*-test was applied. Statistical analysis was conducted using the SPSS (version 15, 2006; SPSS Inc., IBM corporation, Chicago, Illinois, USA) for Windows statistical package. *P* value less than 0.05 was considered statistically significant.

Results

The demographic and preoperative clinical data are shown in Table 1. There was a nonsignificant ($P > 0.05$) difference between studied patients with respect to age, weight, height, BMI, and ASA grade.

Operative data and the result of PO histopathological examination of excised specimens are shown in Table 2. There was nonsignificant ($P > 0.05$) difference between

Table 1 Patients' data and duration of surgery

Data	Group C (*n* = 50)	Group N (*n* = 50)	*P*
Age (years)	60.4 ± 9.5 (33–70)	62.6 ± 8.7 (35–73)	0.215
ASA (I : II : III)	37 : 7 : 6	34 : 11 : 5	0.147
Duration of disease (years)	4 ± 0.7 (3–5)	3.8 ± 0.2 (3.5–4.5)	0.181
Weight (kg)	88 ± 6.8 (73–98)	89.6 ± 5.5 (78–97)	0.330
Height (cm)	169.2 ± 5 (163–182)	169.4 ± 3.3 (165–180)	0.555
BMI (kg/m^2)	30.8 ± 2.8 (23.8–34.5)	31.3 ± 2.1 (25.8–34.5)	0.640

Data are presented as mean ± SD; ratio and ranges are given in parenthesis.

Table 2 Operative data

	Group C (*n* = 50)	Group N (*n* = 50)	*P*
Surgical procedures			
Lobectomy	39 (78)	37 (74)	0.112
Sleeve lobectomy	4 (8)	6 (12)	
Segmentectomy	5 (10)	3 (6)	
Bilobectomy	2 (4)	4 (8)	
Duration of surgery (min)	193.6 ± 22.7 (140–250)	200 ± 25.7 (135–240)	0.175
Duration of lung ventilation (min)	178.4 ± 23.5 (125–215)	180.6 ± 27 (130–225)	0.660
Amount of intraoperative blood loss (ml)	445 ± 123.4 (300–710)	431 ± 93.1 (250–600)	0.672
Type of tumor			
Adenocarcinoma	33 (66)	32 (64)	0.239
Large cell carcinoma	10 (20)	8 (16)	
Squameous cell cancer	7 (14)	10 (20)	

Data are presented as mean ± SD and numbers; ranges and percentages are given in parenthesis.

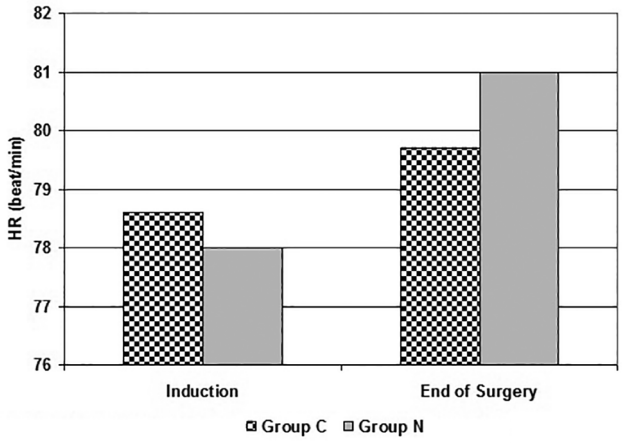
both groups with respect to operative data and the type of tumor.

Hemodynamic measures determined at the time of induction of anesthesia showed nonsignificant (P > 0.05) difference between both study groups; however, both groups showed significant decrease in SAP and mean arterial blood pressure (MAP) measures determined at the end of surgery than at induction measures. Nicotine induced significantly (P = 0.011) higher HR compared with baseline measures in group N with nonsignificantly higher HR compared with group C (Fig. 1). Concomitantly, mean SAP and MAP measures estimated at the end of surgery in group N were significantly (P = 0.039 and 0.026, respectively) higher compared with group C (Table 3 and Fig. 2).

Throughout 48 h after admission to ICU while epidural catheter was still *in situ*, pain VAS scores showed nonsignificant (P > 0.05) difference compared with baseline score determined at the time of ICU admission, in both groups, but with significantly lower scores in group N compared with group C. After removal of epidural catheter and cessation of epidural analgesia, pain VAS scores were significantly higher compared with pain score determined at 48 h after ICU admission, just before epidural catheter removal, in both groups, but with significantly lower scores in group N compared with group C (Fig. 3).

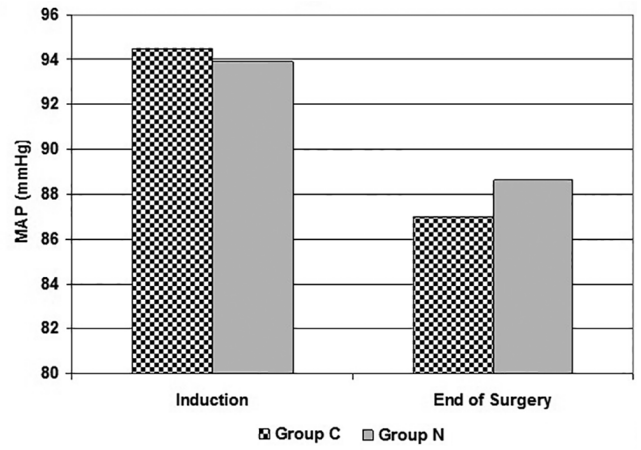
All patients requested rescue analgesia for pain VAS score of four with varied number of requests, with significantly (χ^2 = 5.346, P = 0.012) higher number of requests of rescue analgesia in group C compared with group N (Table 4 and Fig. 4). As a sole analgesic, TNP significantly (χ^2 = 5.223, P = 0.011) reduced the number of requests of rescue analgesia after removal of epidural catheter in comparison with placebo, as

Figure 1



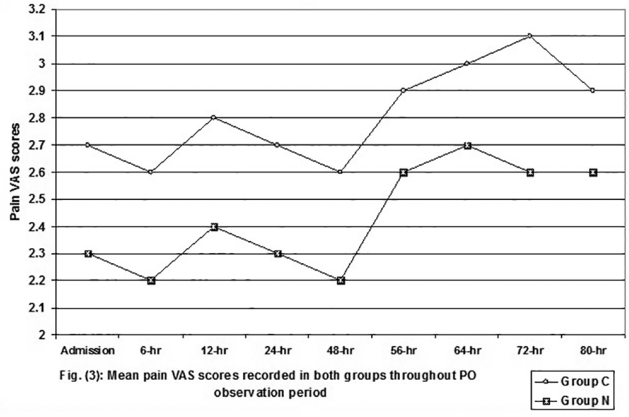
Mean heart rate (HR) determined at the time of induction of anesthesia and at the end of surgery in both studied groups.

Figure 2



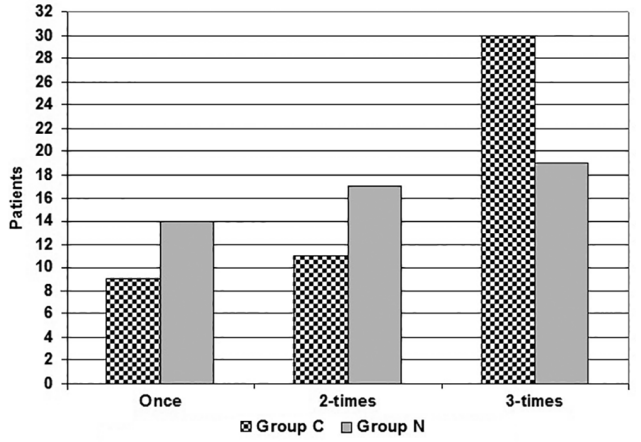
Mean mean arterial blood pressure (MAP) estimated at the time of induction of anesthesia and at the end of surgery in both studied groups.

Figure 3



Mean pain visual analog scale (VAS) scores recorded in both groups throughout the postoperative observation period.

Figure 4



Patients' distribution according to the number of requests of rescue analgesia.

Table 3 Patients' hemodynamic data recorded at the time of induction of anesthesia and at the end of surgery

Data	Time of estimation	Group C (n = 50)	Group N (n = 50)	P
Heart rate (beats/min)	At induction	78.6 ± 4.1	78 ± 4.9	0.698
	At end of surgery	79.7 ± 4.4	81 ± 6	0.239
	P	0.173	0.011	
SAP (mmHg)	At induction	119.4 ± 5.7	118.5 ± 4.7	0.435
	At end of surgery	100.1 ± 3.1	102 ± 3.1	0.039
	P	0.0007	0.0009	
DAP (mmHg)	At induction	82 ± 3.6	81.6 ± 3.1	0.671
	At end of surgery	80.4 ± 3.9	81.9 ± 3.5	0.045
	P	0.013	0.092	
MAP (mmHg)	At induction	94.5 ± 3.1	93.9 ± 2.7	0.396
	At end of surgery	87 ± 2.8	88.6 ± 2.3	0.026
	P	0.0005	0.001	

Data are presented as mean ± SD; DAP, diastolic arterial blood pressure; MAP, mean arterial blood pressure; SAP, systolic arterial blood pressure.

Table 4 Patients' postoperative pain data recorded since admission to ICU until 80 h thereafter

	Group C (n = 50) (%)	Group N (n = 50) (%)	P
After ICU admission (during epidural analgesia)			
At admission	2.7 ± 1	2.3 ± 1.1	0.023
6 h			
Value	2.6 ± 1	2.2 ± 0.9	0.028
P_1	0.619	0.432	
12 h			
Value	2.8 ± 0.7	2.4 ± 0.9	0.019
P_1	0.444	0.839	
24 h			
Value	2.7 ± 0.6	2.3 ± 1.1	0.013
P_1	0.876	0.801	
48 h			
Value	2.6 ± 0.9	2.2 ± 1.1	0.024
P_1	0.607	0.238	
After end of epidural analgesia			
56 h			
Value	2.9 ± 0.7	2.6 ± 0.8	0.022
P_2	0.017	0.026	
64 h			
Value	3 ± 0.8	2.7 ± 0.9	0.041
P_2	0.005	0.018	
72 h			
Value	3.1 ± 1	2.6 ± 1.2	0.029
P_2	0.027	0.034	
80 h			
Value	2.8 ± 0.7	2.6 ± 0.8	0.035
P_2	0.067	0.028	
Number of requests of rescue analgesia			
Once	9 (18)	14 (28)	0.012
Two times	11 (22)	17 (34)	
Three times	30 (60)	19 (38)	
Total number	121	105	0.011
Number/ patient	2.42	2.1	

Data are presented as mean ± SD. P, significance between groups N and C; P_1, significance versus at admission pain visual analog scale (VAS) score; P_2, significance versus 48 h pain VAS scores.

there were 105 requests (2.1 times/patient) of rescue analgesia in group N compared with 121 requests (2.42 times/patient) in group C since the removal of epidural catheter until the end of 80 h PO follow-up (Fig. 5).

During PO observation period, 25 patients developed PONV, 18 in group N and seven in group C, with significantly higher (χ^2 = 7.916, P = 0.01) frequency of PONV in group N compared with group C.

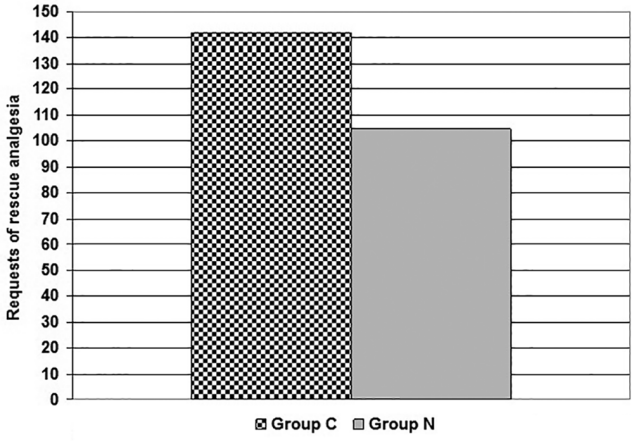
Discussion

This study demonstrated that transdermal nicotine significantly reduced pain VAS scores compared with control in thoracotomy patients. Pain VAS scores were significantly higher compared with pain score determined at 48 h after ICU admission. Patients requested rescue analgesia for pain VAS score of 4 with varied number of requests, with significantly higher number in the control group compared with the nicotine group. Nicotine also reduced the number of requests of rescue analgesia required.

The current study was based on a selective basis to equalize intragroup difference and to allow evaluation of the effect of the study drug. All patients were chosen to be male patients because of difference in pain thresholds between both genders, which was previously proved to be significantly higher in female patients who mostly consume more rescue analgesia than in male patients and was attributed to higher levels of apprehension [16,17]. Current smokers were excluded from the study depending on the previous study by Olson *et al.* [18] who indicated that transdermal nicotine, 5–15 mg, failed to relieve PO pain or reduce opioid use in smokers. In addition, Richardson *et al.* [19] documented that the analgesic or enhanced nociceptive effect of nicotine may depend on tobacco use history.

Thoracic epidural injection of bupivacaine was chosen as the modality for provision of intraoperative and PO

Figure 5



Number of requests of rescue analgesia after removal of the epidural catheter.

rescue analgesia in both study groups for its previously proven efficacy for control of post-thoracotomy pain [20,21] and for equalization of the baseline effect between both groups; hence, the difference could be attributed to the study drug. Ceftriaxone, a β-lactam antibiotic, was used as antibiotic prophylaxis after induction of anesthesia and was continued postoperatively. The choice of ceftriaxone was dependent on the experimental evidence that β-lactam antibiotics offer neuroprotection by increasing glutamate transporter expression and prevent the development of tolerance and dependence to opioid [22]. This effect was further documented experimentally for nicotine where Schroeder *et al.* [23] suggested that glutamate transporter subtype 1 activation enhances and preserves nicotine antinociception and documented that β-lactam antibiotics could be used as potential complementary therapeutic agents for the treatment of chronic pain.

The current study demonstrated significantly lower PO pain VAS scores in patients who received nicotine patch compared with those who received placebo, either during epidural infusion or after its cessation. Consumption of rescue analgesia as a measure for analgesic efficacy was also significantly lower in the nicotine group compared with the placebo group.

These findings supported those previously documented concerning antinociceptive effect of nicotine, irrespective of form of administration; Flood and Daniel [24] found that treatment with a single dose of nicotine immediately before emergence from anesthesia was associated with significantly lower pain scores during the first day after surgery in association with a reduction in morphine utilization. Hong *et al.* [25] documented that patients treated with nicotine reported significantly lower pain scores when compared with those treated with placebo during the first hours after surgery and for 5 days after surgery. In addition, Habib *et al.* [26] found that patients who underwent radical retropubic prostatectomy and who were treated with nicotine showed significantly lower cumulative morphine consumption at 24 h.

Yagoubian *et al.* [27] documented that preoperatively administered nicotine nasal spray (3 mg) was associated with a highly significant decrease in pain reported during the 5 days after third molar surgery. Jankowski *et al.* [28] reported that intraoperative use of intranasal nicotine has a sustained opioid-sparing effect in nonsmoking women undergoing gynecological procedures. Vibe Nielsen *et al.* [29] presented seven studies of which six showed an effect of nicotine on PO pain when given at a low dose, with short time of exposure and to nonsmokers.

As an indirect evidence for the analgesic effect of nicotine, Steinmiller *et al.* [30] found that the number of patients who received opioids during PO recovery before patient-controlled analgesia (PCA) was higher among patients who were acutely smoking abstinent than nonsmokers, and during PCA abstinent smokers had significantly more injection denials than nonsmokers and concluded that acute nicotine abstinence during hospitalization increases PCA opioid medication seeking. Richardson *et al.* [31] documented that nonsmokers with spinal cord injury showed a reduction in mixed forms of pain following nicotine exposure. Sindhu *et al.* [32] failed to demonstrate analgesic effect of choline, which is a selective agonist at α7-type nicotinic receptors that does not have addictive or sympathetic activating properties, and attributed this failure to the absence of an anti-inflammatory effect secondary to inadequate reduction in tumor necrosis factor plasma levels. Umana *et al.* [33] documented that, along with their well-known role in nicotine addiction and autonomic physiology, neuronal nicotinic receptors also have profound analgesic effects in animal models and humans, and analgesics that target specific neuronal nicotinic receptor subtypes have shown highly efficacious antinociceptive properties in acute and chronic pain models.

In contrast to these results, the systematic review conducted by Mishriky and Habib [34] suggests that perioperative nicotine administration was associated with a statistically insignificant reduction in pain scores at 24 h but with statistically significant reduction in cumulative opioid consumption at 24 h, an effect that seemed to be limited to nonsmokers, and concluded that these data do not support a role for nicotine in perioperative analgesia. However, the results of this

meta-analysis was limited by the heterogenicity of studies collected, as among the included nine studies TNP was used in six studies and nicotine nasal spray in three studies; hence, the effect of route of administration was neglected and TNP as a slow-release form surely provide different nicotine blood level and subsequent longer duration of action. Four studies recruited only women; hence, the difference of pain threshold between male patients and female patients may induce bias of the determined scores. Moreover, two studies recruited smokers who were settled, as previously mentioned, and showed no effect for TNP on their pain sensation. Finally, the included studies evaluated pain scores during only 24 h; in the current study pain scores determined during this period of immediate PO was nonsignificant between nicotine and placebo patches; however, the effect was pronounced later on, a finding indicating cumulative effect of TNP, which could be considered as another limitation for this meta-analysis.

The sympathetic activating properties of nicotine with concomitant tachycardia and elevation of blood pressure was found to be advantageous for competing epidural sympatholytic effect, and hence minimized decrease in blood pressure. Unfortunately, nicotine administration resulted in significantly higher frequency of PONV and requirement for antiemetics; however, the frequency of occurrence of PONV was coincident with that previously reported in the literature; Habib *et al.* [26] found that the maximum nausea verbal rating scale score was significantly higher in the nicotine than in the placebo group. Vibe Nielsen *et al.* [29] documented that nicotine seems to increase the occurrence of nausea and vomiting.

The obtained results and review of the literature allowed concluding that TNP could be considered as appropriate adjuvant analgesic modality to thoracic epidural bupivacaine analgesia for patients who had thoracotomy during early PO period and could be used as the sole analgesic modality after cessation of epidural analgesia. Prophylactic antiemetics were advocated to guard against the high possibility of development of nausea and/or vomiting after application of TNP. Wider scale studies to evaluate the effect of TNP as the sole analgesic during and after simpler surgical procedures are recommended.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

1 Wildgaard K, Ringsted TK, Ravn J, Werner MU, Kehlet H. Late sensory changes following chest drain insertion during thoracotomy. Acta Anaesthesiol Scand 2013; 57:776–783.

2 Maguire MF, Ravenscoft A, Beggs D, Duffy JP. A questionnaire study investigating the prevalence of the neuropathic component of chronic pain after thoracic surgery. Eur J Cardiothorac Surg 2006; 29:800–805.

3 Wildgaard K, Ravn J, Nikolajsen L, Jakobsen E, Jensen TS, Kehlet H. Consequences of persistent pain after lung cancer surgery: a nationwide questionnaire study. Acta Anaesthesiol Scand 2011; 55:60–68.

4 Rabanal Llevot JM, Fayad Fayad M, Bartolomé Pacheco MJ, Carceller Malo JM, Naranjo Gómez S, Ortega Morales J. Continuous paravertebral block as an analgesic method in thoracotomy. Cir Esp 2010; 88:30–35.

5 Momenzadeh S, Elyasi H, Valaie N, Radpey B, Abbasi A, Nematollahi F, Mohammadinasab H. Effect of cryoanalgesia on post-thoracotomy pain. Acta Med Iran 2011; 49:241–245.

6 Gupta SD, Mitra K, Mukherjee M, Roy S, Sarkar A, Kundu S, *et al.* Effect of magnesium infusion on thoracic epidural analgesia. Saudi J Anaesth 2011; 5:55–61.

7 Grider JS, Mullet TW, Saha SP, Harned ME, Sloan PA. A randomized, double-blind trial comparing continuous thoracic epidural bupivacaine with and without opioid in contrast to a continuous paravertebral infusion of bupivacaine for post-thoracotomy pain. J Cardiothorac Vasc Anesth 2012; 26:83–89.

8 Shi Y, Weingarten TN, Mantilla CB, Hooten WM, Warner DO. Smoking and pain: pathophysiology and clinical implications. Anesthesiology 2010; 113:977–992.

9 Rowley TJ, Payappilly J, Lu J, Flood P. The antinociceptive response to nicotinic agonists in a mouse model of postoperative pain. Anesth Analg 2008; 107:1052–1057.

10 Costa R, Motta EM, Manjavachi MN, Cola M, Calixto JB. Activation of the alpha-7 nicotinic acetylcholine receptor (α7 nAchR) reverses referred mechanical hyperalgesia induced by colonic inflammation in mice. Neuropharmacology 2012; 63:798–805.

11 Makó S, Stampf G. Transdermal therapeutic systems. Acta Pharm Hung 2001; 71:293–299.

12 Gentile A, Tran-Van D, Dardare E, Fritsch N, Benois A, Fontaine B. Management of transdermal therapeutics in perioperative care. Ann Fr Anesth Reanim 2009; 28:311–320.

13 Wirz S, Wittmann M, Schenk M, Schroeck A, Schaefer N, Mueller M, *et al.* Gastrointestinal symptoms under opioid therapy: a prospective comparison of oral sustained-release hydromorphone, transdermal fentanyl, and transdermal buprenorphine. Eur J Pain. 2009; 13:737–743.

14 Huskisson EC. Measurement of pain. Lancet 1974; 2:1127–1131.

15 Kraemer HC, Theimann S. *How many subjects? Statistical power analysis in research*. Newbury Park, CA: Sage; 1987.

16 Hussain AM, Khan FA, Ahmed A, Chawla T, Azam SI. Effect of gender on pain perception and analgesic consumption in laparoscopic cholecystectomy: an observational study. J Anaesthesiol Clin Pharmacol 2013; 29:337–341.

17 Zeidan A, Al-Temyatt S, Mowafi H, Ghattas T. Gender-related difference in postoperative pain after laparoscopic Roux-En-Y gastric bypass in morbidly obese patients. Obes Surg 2013; 23:1880–1884.

18 Olson LC, Hong D, Conell-Price JS, Cheng S, Flood P. A transdermal nicotine patch is not effective for postoperative pain management in smokers: a pilot dose-ranging study. Anesth Analg 2009; 109:1987–1991.

19 Richardson EJ, Ness TJ, Redden DT, Stewart CC, Richards JS. Effects of nicotine on spinal cord injury pain vary among subtypes of pain and smoking status: results from a randomized, controlled experiment. J Pain. 2012; 13:1206–1214.

20 Salengros JC, Huybrechts I, Ducart A, Faraoni D, Marsala C, Barvais L, *et al.* Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. J Cardiothorac Vasc Anesth 2010; 24:608–616.

21 Kanazi GE, Ayoub CM, Aouad M, Abdallah F, Sfeir PM, Adham AB, El-Khatib MF. Subpleural block is less effective than thoracic epidural analgesia for post-thoracotomy pain: a randomised controlled study. Eur J Anaesthesiol 2012; 29:186–191.

22 Rawls SM, Tallarida R, Robinson W, Amin M. The beta-lactam antibiotic, ceftriaxone, attenuates morphine-evoked hyperthermia in rats. Br J Pharmacol 2007; 151:1095–1102.

23 Schroeder JA, Quick KF, Landry PM, Rawls SM. Glutamate transporter activation enhances nicotine antinociception and attenuates nicotine analgesic tolerance. Neuroreport 2011; 22:970–973.

24 Flood P, Daniel D. Intranasal nicotine for postoperative pain treatment. Anesthesiology 2004; 101:1417–1421.

25 Hong D, Conell-Price J, Cheng S, Flood P. Transdermal nicotine patch for postoperative pain management: a pilot dose-ranging study. Anesth Analg 2008; 107:1005–1010.

26 Habib AS, White WD, El Gasim MA, Saleh G, Polascik TJ, Moul JW, Gan TJ. Transdermal nicotine for analgesia after radical retropubic prostatectomy. Anesth Analg 2008; 107:999–1004.

27 Yagoubian B, Akkara J, Afzali P, Alfi DM, Olson L, Conell-Price J, *et al.* Nicotine nasal spray as an adjuvant analgesic for third molar surgery. J Oral Maxillofac Surg 2011; 69:1316–1319.

28 Jankowski CJ, Weingarten TN, Martin DP, Whalen FX, Gebhart JB, Liedl LM, *et al.* Randomised trial of intranasal nicotine and postoperative pain, nausea and vomiting in non-smoking women. Eur J Anaesthesiol 2011; 28:585–591.

29 Vibe Nielsen S, Petersen RH, Pachai A. A possible analgesic effect of nicotine on postoperative pain. Ugeskr Laeger 2012; 174:1594–1598.

30 Steinmiller CL, Diederichs C, Roehrs TA, Hyde-Nolan M, Roth T, Greenwald MK. Postsurgical patient-controlled opioid self-administration is greater in hospitalized abstinent smokers than nonsmokers. J Opioid Manag 2012; 8:227–235.

31 Richardson EJ, Richards JS, Stewart CC, Ness TJ. Effects of nicotine on spinal cord injury pain: a randomized, double-blind, placebo controlled crossover trial. Top Spinal Cord Inj Rehabil 2012; 18:101–105.

32 Sidhu N, Davies S, Nadarajah A, Rivera J, Whittington R, Mercier RJ, *et al.* Oral choline supplementation for postoperative pain. Br J Anaesth 2013; 111:249–255.

33 Umana IC, Daniele CA, McGehee DS. Neuronal nicotinic receptors as analgesic targets: it's a winding road. Biochem Pharmacol 2013; 86:1208–1214.

34 Mishriky BM, Habib AS. Nicotine for postoperative analgesia: a systematic review and meta-analysis. Anesth Analg 2014; 119:268–275. [Epub ahead of print]