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Pre-emptive Use of Transdermal Nicotine Patch in Lumber Disc Surgery: It's Effects on Intraoperative Anaesthetic and Analgesic Requirements, Haemodynamics and Postoperative Analgesia

[1]Ashgan Raouf Ali, [2]Sameh Ahmed Sakr

[1]Anaesthesiology Department, [2]Neurosurgery Department.
Cairo University, Faculty of Medicine,

Abstract: Nicotine has been reported to have analgesic effects in animal and human studies. This study evaluated the effect of pre-emptive use of transdermal nicotine patch on intraoperative sevoflurane and fentanyl requirements, perioperative haemodynamics and postoperative analgesia in patients undergoing lumber disc surgery. Fifty non-smokers patients (ASA I and II) undergoing lumber discectomy were randomly allocated to receive either 7 mg nicotine patch (nicotine group n=25) or placebo patch (control group n=25) two hours before surgery. The anaesthetic technique was identical in both groups. All operations were done by the same surgeon. Intraoprative fentanyl requirement and sevoflurane concentration needed to maintain bispectral index between 40-50 were evaluated. Patients used a patient controlled analgesia device to receive bolus dose of morphine after surgery. Perioperative haemodynamics (mean arterial pressure and heart rate), cumulative morphine consumption, pain scores, sedation scores and respiratory rate were measured for 24 hours postoperatively. Incidence of adverse effects and patients' satisfaction with their pain management were also recorded. Nicotine patch application resulted in significant reduction of intraoperative fentanyl requirement and postoperative cumulative morphine consumption at 8, 12, and 24 hours ($P<0.05$). The groups were similar with respect to sevoflurane requirement, perioperative haemodynamics, postoperative sedation scores and pain scores measured in supine or sitting position. Number of patients experienced postoperative respiratory depression (respiratory rate<10 breath/min) and itching was significantly higher in control group than nicotine group ($P<0.05$). The incidence of postoperative nausea and vomiting, and number of patients receiving antiemetic treatment in the first postoperative 24 h were reduced in nicotine group than control group but this reduction was statistically insignificant ($P>0.05$). Patient satisfaction was better in nicotine group compared with the control group ($p=0.05$). Pre-emptive application of 7 mg transdermal nicotine patch provided significant reduction of intra- and post-operative opioid requirements associated with decreased incidence of opioid related adverse effects in patients undergoing lumber disc surgery. However, it had no effect on sevoflurane requirement or perioperative haemodynamics.

Key words: Transdermal nicotine, analgesia, lumber laminectomy.

INTRODUCTION

The concept of pre-emptive analgesia, which is an analgesic treatment initiated before the surgical procedure, was introduced to protect the central nervous system from deleterious effects of noxious stimuli, and the patient from the resulting allodynia, and increased pain (Kissin, 2000).

Although opioid analgesics are the most frequently used drugs for post-operative analgesia, the use of opioid is limited by side-effects and by the fact that certain types of pain respond poorly to opioid (Dickenson, 1994). Because of the multiple mechanisms involved in postoperative pain, a multimodal analgesia regimen, with a combination of opioid and nonopioid analgesic drugs must be used to enhance analgesic efficacy and reduce opioid requirements and side effects (Habib *et al*., 2005).

Nicotine, the primary psychoactive component of cigarette smoke, produces its pharmacological effects by stimulating central nicotinic (acetylcholine) receptors (Dani and De Biasi, 2001). These receptors may play a role in modulating pain transmission within the central nervous system (Damaj *et al*., 2000). Nicotinic agonists have been shown to have antinociceptive properties in several animal models (Carstens *et al*., 2001; Le Novere

Corresponding Author: Ashgan RA, Cairo University, Faculty of Medicine, Anaesthesiology Department,
E-mail: ashganraouf@yahoo.com

et al., 2002; Caggiula, 1995). Previous studies in human volunteers have shown that nicotine has a mild to moderate analgesic effects in such diverse modalities of pain. (Pauli *et al*., 1993; Jamner *et al*., 1998).

Recently some clinical studies evaluated the effect of intranasal or transdermal nicotine application in postoperative pain control and they reported that, nicotine administration decreased postoperative pain scores and opioid consumptions (Flood and Daniel, 2004; Hong *et al*., 2008; Habib *et al*., 2008). Another study done by Turan *et al*. (2008) failed to detect any analgesic effect of perioperative transdermal nicotine administration. The present study was designed as randomized double blinded controlled study to evaluate the efficacy of pre-emptive usage of a 7 mg nicotine patch in patients undergoing lumber disc surgery as regards intraoperative sevoflurane and fentanyl requirements, perioperative haemodynamics and postoperative analgesia.

MATERIAL AND METHODS

After approval of the Local Ethics Committee, an informed consent was obtained from all patients. Fifty adult non-smokers patients, 20-60 years of age, ASA physical status I and II, scheduled to undergo elective lumbar discectomy surgery were studied in Kasr El-Aini Hospital from September 2008 to March 2009. Exclusion criteria included current or recent smoking history within the last 6 months, a history of uncontrolled hypertension, ischemic heart disease, peripheral vascular disease, arrhythmias, respiratory disease, stroke, diabetes, chronic pain, or use of chronic pain medications. The night before surgery all patients were taught how to use patient controlled analgesia (PCA) device and how to assess their pain using a 100 points visual analogue scale (VAS), with 0 representing no pain at all and 100 representing the worst imaginable pain. Patients were randomly allocated according to computer-generated randomization to two equal groups (n = 25). Nicotine group received transdermal nicotine patch 7mg (Nicotinell® TTS 10 cm^2 releasing 7 mg /24 h, Novartis, SA Nyon, Switzerland), and the control group received identical placebo patch. All patches were placed on patient's upper arm and covered with a sterile gauze and tape by an anaesthesiology resident not involved in the data collection process two hours before surgery. All patients were premedicated with i.v. 0.02 mg/kg midazolam in the holding area. Upon arrival to the operating room (OR) i.v infusion of 5 ml/kg Lactated Ringer's solution was given for all patients before induction of anaesthesia. Baseline heart rate (HR), mean arterial pressure (MAP) and oxygen saturation (Spo_2) were recorded after the placement of routine monitors (Infinity SC 8000, Dräger medical system, Avenue, Danvers, MA, USA). In all study patients, a standard BIS® monitor strip (BISX®, Aspect medical Systems, Norwood, MA, USA) were placed on the forehead, and a baseline value of BIS was recorded before induction of general anaesthesia.

After preoxygenation, general anaesthesia was induced in all patients with intravenous fentanyl 1µg/kg, propofol 2 mg/kg and lidocaine 0.5 mg/kg to reduce pain on injection. Endotracheal intubation was facilitated with vecuronium 0.08 mg/kg. General anaesthesia was maintained with, sevoflurane in 100% oxygen, fentanyl 1 µg/kg/h, and vecuronium. All patients were mechanically ventilated to maintain end-tidal carbon dioxide between 35 to 40 mm Hg. Sevoflurane concentration was titrated to achieve a target BIS value between 40 and 50. In all cases, the aim was to maintain MAP and HR within 80-120% of their baseline values. Intra-operative fentanyl infusion rate was changed according to HR and MAP measurements after correlation with the BIS value. MAP or HR rise of more than 20% of baseline values during anaesthesia while BIS value was between 40-50, was assumed to be due to insufficient analgesia and the dose of fentanyl was increased by 0.5µg/kg/h. MAP drop of more than 20% below baseline was treated initially with iv crystalloids and 50% decrements in fentanyl infusion rate. Atropine 0.5 mg was administered in case of bradycardia (HR<45 beat/min). If the BIS value became less than 40 for more than 30 second the concentration of sevoflurane was decreased by 25%. If BIS value exceeded 50 for more than 30 second the concentration of sevoflurane was increased by 25%.

All operations were done by the same surgeon. The patients were turned to a prone position on the standard operating table, where eyes, airway, and pressure point were checked, supported and protected. Skin incision was made in the middle of the back over the area being operated on. The incision was deepened to the muscles which were spread outwards to reveal the laminae. The correct level was confirmed either by counting from a fixed point, or taking an x-ray. Having exposed the laminae, the bone was nibbled away using a variety of bone cutters. Little was removed for a simple slipped disc operation, while a great deal of bone will be taken to decompress the spine for canal stenosis. Having completed the planned operation and stopped the bleeding, the muscles were sewn up and the skin was closed by subcutecular stitches.

At completion of surgery inhalational anaesthetic was discontinued, fentanyl infusion was stopped, and residual neuromuscular block was antagonized with atropine 0.02 mg/kg and neostigmine 0.08 mg/kg.

MAP and HR were recorded upon arrival in the operating room (baseline), before induction of general anaesthesia and intraoperatively every 5 minutes. BIS value and end-tidal sevoflurane concentration were recorded intraoperatively every 5 minutes. The total amount of fentanyl administered during operation was also recorded.

After tracheal extubation, patients were transferred to the post anaesthesia care unit (PACU) where oxygen saturation was continuously measured by pulse oximeter. Oxygen 2–4 L/min via nasal probe was administered to maintain an oxygen saturation of more than 95%. Each patient was reminded of how to operate a PCA system (P 5000 IVAC-PCAM, Alaris Medical System, Hampshire, UK) after receiving an initial bolus of morphine 3 mg iv, and was followed for 24 h by the study nurses who were blinded to the study protocol. The PCA device was set to deliver 2 mg of morphine with a lock-out interval of 15 min and a 4h limit of 35 mg, and no continuous infusion. If analgesia was inadequate (VAS pain scores >50) at any time during the study period, the lock-out time was shortened to 10 min. The time interval from PACU admission to the first analgesic PCA demand was recorded for all patients.

Each patient stayed in the PACU for two hours, and was transferred thereafter to the ward. Pain scores VAS (measured in supine and sitting position),MAP, HR, sedation scores (modified Ramsay sedation scale, Table 1) and morphine consumption were assessed every 30 minutes in the PACU, and at 4, 8, 12 and 24 hours postoperatively on the ward.

Occurrence of any postoperative side effects [such as nausea, vomiting, urinary retention, constipation, dizziness, somnolence, blurred of vision, dry mouth, pruritus or respiratory depression (RR< 10 breath/min)] was also recorded. If the patients experienced sustained nausea or vomiting, ondansetron (4 mg IV) was given as a rescue antiemetic.

If a respiratory rate of <10 per minute for a period longer than 10 min was observed, the PCA pump was stopped until a respiratory rate of 10 per minute was reached. The PCA regimen was then restarted using a PCA bolus of 0.5 mg less than the previous one.

At 24 hours, patients satisfaction with the postoperative pain management was assessed using 100-point verbal rating scale (VRS), with 1= highly dissatisfied to 100= completely satisfied. All measurements were recorded by a research assistant who was blinded to group allocation.

A sample size of 25 patients per group was calculated to be required to detect a significant difference of 15% or more in PCA (usage) morphine consumption with a power of 85% and a significance level of 0.05.

Statistical Analysis:

Data were presented as mean (SD) or number (%) as appropriate. Comparison between the two groups was performed using unpaired student's t test. Intra group comparisons relative to baseline were performed using repeated measure analysis of variance (ANOVA) with post hoc Dunnet's test if ANOVA results were significant. Categorical variables were compared using test of proportion. A P value less than 0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Sixty nine patients were assessed for study eligibility (12 patients failed to meet the inclusion criteria and 7 patients refused to sign the consent form). The remaining 50 consenting patients who fulfilled the entry criteria were enrolled in this study. All patients were able to complete the entire study and their data were included in final analysis. Demographic and intraoperative outcomes are shown in Table 2. The two groups were similar with respect to age, sex, body weight, height, proportions of ASA I and ASA II patients and duration of surgery. The mean amount of intraoperative fentanyl dose administered in nicotine group was significantly lower than that in control group [192 (20.1) µg versus 256 (23.4) µg, respectively; P< 0.05). End-tidal sevoflurane concentration (adjusted to maintain a BIS value of 40–50) was comparable in both groups. The times from PACU admission to first analgesic (PCA) demand were significantly longer in the nicotine group than the control group [16.7(3.1) min in nicotine group versus 7.5(2.05) min in control group; P < 0.05]. VAS pain scores recorded on supine or sitting position were comparable in both groups at each time point assessed in the PACU and on the ward after surgery (Fig. 1, 2).

Compared with the control group, PCA morphine consumption was reduced in nicotine group during the first postoperative 24 h. The reduction was statistically significant from the eighth postoperative hour till the end of study, P <0.05 (Fig. 3).

Inter-group and intra-group comparisons of the HR and MAP showed no significant differences at all time intervals in both groups (Table 3).

Ramsay score also showed no significant difference between the two groups and was maintained between 2 and 3 during the postoperative study period.

The incidence of postoperative side effects was comparable in the two groups except for itching and respiratory depression (Table 4). The number of patients experienced itching and respiratory depression were significantly higher in the control group than the nicotine group [10 (40%) and 4 (16%) versus 3 (12%) and 0(0%) respectively, P<0.05].

Incidence of postoperative nausea and vomiting, number of patients receiving antiemetic treatment and number of ondansetron injections required in the first postoperative 24 h were reduced in nicotine group than control group but this reduction was not statistically significant P>0.05 (Table 4).

Regarding patient satisfaction (VRS, 1-100), nicotine group showed higher scores than control group but this difference was marginal significant; p=0.05 (Table 4).

Table 1: Modified Ramsay scale for sedation. (Ramsay *et al.*, 1974)

Score	Description
1	Anxious and agitated or restless, or both
2	Cooperative, oriented and tranquil
3	Drowsy, but responds to commands
4	Asleep, brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to light glabellar tap or loud auditory stimulus
6	Asleep and unarousable

Table 2: Demographic and intraoperative data of both groups [mean (SD), number or ratio].

	Control group (n = 25)	Nicotine group (n = 25)
Age (years)	47 (7)	45 (6)
Sex (M/F)	14/11	15/10
ASA status (I/II)	12/13	14/11
Weight (kg)	70 (9)	69 (10)
Height (cm)	160 (6)	162 (4)
Duration of surgery (min)	110 (26)	107 (25)
Intraoperative fentanyl (µg)	256 (23.4)	192 (20.1)*
End-tidal sevoflurane (%)	1.92 (0.34)	1.88 (0.31)

ASA = American Society of Anaesthesiologists. * P < 0.05 compared with the control group.

Table 3: Peri-operative haemodynamic data in both groups. [mean (SD)].

	Control group (n = 25)		Nicotine group (n = 25)	
	HR(beat/min)	MAP (mmHg)	HR (beat/min)	MAP (mmHg)
Baseline	80.2 (9.1)	90.3 (10.7)	81.3 (12.4)	91.4 (11.2)
Pre-induction	81.3 (11.2)	91.4 (8.1)	83.3 (13.2)	92.3 (12.1)
Intra-operative	77.1 (9.2)	80.2 (7.1)	85.1 (10.1)	82.3 (8.2)
30 min postoperative	85.3 (17.1)	85.3 (8.4)	89.2 (18.3)	87.2 (8.1)
60 min postoperative	83.4 (16.3)	87.2 (9.2)	85.4 (17.1)	90.3 (7.4)
90 min postoperative	82.2 (15.1)	90.3 (8.4)	84.3 (16.2)	92.5 (8.3)
120 min postoperative	82.4 (12.2)	93.3 (7.2)	85.2(14.1)	95.4 (9.4)
4 h postoperative	81.3(14.1)	94.3 (9.1)	84.3 (15.2)	96.1 (8.4)
8 h postoperative	78.2(13.3)	94.2 (7.3)	83.3 (13.1)	97.4 (7.1)
12 h postoperative	80.4 (13.2)	93.2 (8.4)	84.2 (12.4)	96.1 (7.3)
24 h postoperative	79.2 (10.3)	86.2 (6.1)	80.5 (11.4)	88.1 (8.2)

HR= heart rate; MAP= mean arterial pressure, Intra-operative = weighted mean of intra-operative readings.

Table 4: Postoperative data of both groups. [mean (SD) or number (%)]

	Control group (n = 25)	Nicotine group (n = 25)
Time to first analgesic PCA demand (min)	7.5 (2.05)*	16.7 (3.1)
Incidence of postoperative side effects [n (%)]		
Nausea	12 (48%)	8(32%)
Vomiting	10 (40%)	7(28%)
Dizziness	4 (16%)	2 (8%)
Somnolence	2 (8%)	1 (4%)
Itching	10 (40%)*	3 (12%)
Blurred vision	0 (0%)	0 (0%)
Urinary retention	1 (4%)	0 (0%)
Dry mouth	1 (4%)	0 (0%)
Constipation	2 (8%)	1 (4%)
Respiratory depression	4 (16%)*	0 (0%)
Patients receiving antiemetic [n (%)]	12 (48%)	8(32%)
Antiemetic doses (n)	15	12
Patients satisfaction VRS (1-100)	80(11)	94(2)**

* P < 0.05 compared with the nicotine group.

** P=0.05 compared with the control group.

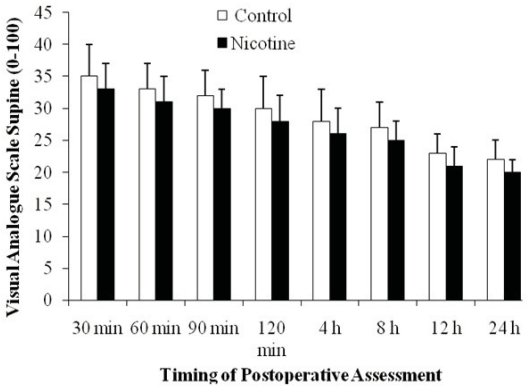

Fig. 1: Postoperative visual analogue scale with patients in the supine position in both groups. Values are means and error bares represent standard deviation.

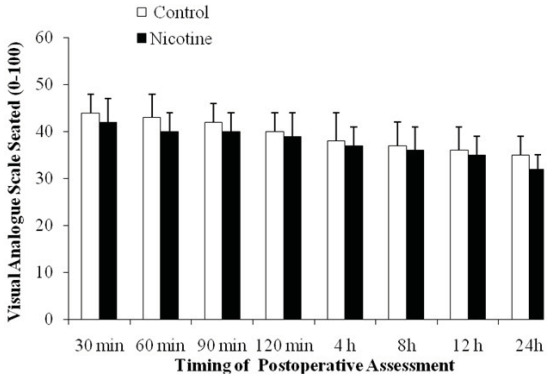

Fig. 2: Postoperative visual analogue scale with patients in the sitting position in both groups. Values are means and error bares represent standard deviation.

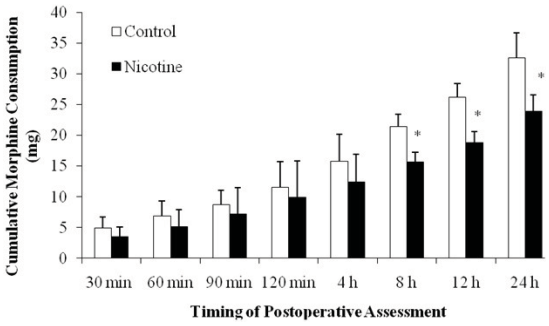

Fig. 3: Postoperative cumulative morphine consumption in both groups. Values are means and error bares represent standard deviation. * P<0.05 versus control group.

Discussion

The present randomized, double blinded, placebo-controlled study, demonstrated that pre-emptive application of transdermal 7 mg nicotine patch 2 hours before surgery, had an analgesic effect in patients undergoing lumber disc surgery. It reduced the intra-operative fentanyl requirement and postoperative cumulative morphine consumption, and led to improved pain control, better patient satisfaction and reduction in opioid related side effects.

The analgesic effects of nicotine observed in the present study correlate well with previous finding in both animals and humans. Experiments with various pain models in animals have shown that, nicotine possess a

variable antinociceptive effects (Block *et al*., 1993; Damaj *et al*., 1994; Carstens *et al*., 2001). In human, dose-dependent increases of pain tolerance, threshold or both have been reported with smoking as a function of nicotine content (Pauli *et al*., 1993).

The antinociceptive effect of nicotine is mediated via activation of neuronal nicotinic acetylcholine receptors (nAChRs) at ligand-gated ion channels (Le Novere *et al*., 2002). Li and Eisenach (2002) reported that, stimulation of α_4 β_2 nAChRs located on noradrenergic terminals may produce analgesia by stimulating spinal norepinephrine release. Activation of α_7 nicotinic receptors located in the central nervous system has also been shown to elicit antinociceptive effects in some acute pain models (Damaj *et al*., 2000). The spinal cholinergic system is also alleged to play an important role in the analgesic action of i.v morphine. Morphine activates a descending inhibitory system, leading to increased release of endogenous acetylcholine in the spinal cord, thereby producing analgesia through activation of spinal muscarinic and nicotinic receptors (Chen and Pan, 2001). Endogenous opioid peptides and μ-opioid receptor activation have also been reported to mediate the antinociceptive properties of nicotine (Berrendero *et al*., 2005; Simon *et al*., 2005). Therefore, the excellent analgesic effect of nicotine in the present study may be attributed to an additive effect of nicotine or synergistic effect with PCA morphine used in postoperative period.

Multiple factors complicate the interaction of pain, gender, and antinociception. Gender specific differences in response to the analgesic effect of nicotine have been reported in both animal and human studies (Craft, 2003). Jamner and colleagues (1998) found that a nicotine patch increased pain thresholds in men but not in women. On the other hand, Girdler *et al*. (2005) reported that female smokers have decreased pain sensitivity to ischemic pain, whereas male smokers have decreased pain sensitivity to cold pressor pain. Although the current study was not powered for a subgroup analysis of gender, its results showed that nicotine was effective in a combined cohort of men and woman patients with insignificant difference between them. This result could be explained by the insufficient number of male and female in both groups.

The present study was designed to administer nicotine via transdermal patch to ensure continuous delivery of the drug over a 24-h period, and a dose of 7 mg nicotine was used, since this dose was tolerated by non-smokers without producing nausea or other adverse effects as stated by Jamner *et al*., in 1998.

To evaluate the level of anaesthesia in clinical practice there is no simple tool available that can distinctly and independently assess antinociception and hypnosis because these variables are closely inter-related and the degree of analgesia may affect the level of hypnosis (Casati *et al*., 2002). BIS monitor was used in the present study to assess level of anaesthesia and to differentiate between inadequate anaesthetic requirements and lack of analgesia.

The application of transdermal nicotine patch, in the current study, significantly decreased the intraoperative fentanyl requirement, while the end-tidal sevoflurane, required to achieve same level of hypnosis (BIS value of 40-50), were comparable between the two groups. The previous findings did not match with what was reported by other researchers who investigated the effect of transdermal nicotine patches in surgical patients and concluded that, the transdermal nicotine had no effect on intraoperative analgesic requirements (Hong *et al*., 2008; Habib *et al*., 2008; Turan *et al*., 2008). The discrepancy between the results of the present study and the other studies may be attributed to the differences in timing of patch application. In the present study, the pre-emptive transdermal application of nicotine patch approximately two hours before surgery appeared rational in order to attain maximal plasma concentration at the time of surgical stimuli, since the peak plasma nicotine concentration reaches approximately at 150-210 min after application of the patch (Fant *et al*., 2000). The other studies applied the patch either, immediately before induction of anaesthesia as in Hong *et al*. study, or one hour before induction as in Habib *et al*. and Turan *et al*. studies, so the serum nicotine did not reach its peak value in the intraoperative period.

Concerning the postoperative analgesia, transdermal nicotine application in the present work provided good analgesia for at least 24 hours after spinal surgery. It was evidenced by delayed first analgesic rescue and significantly less cumulative PCA morphine consumption in the nicotine group versus the control group.

Despite there was no differences in the VAS pain score (recorded in supine and sitting position) between the two groups at any point of assessment after surgery, the patients in the control group required a significant higher amount of morphine to achieve this analgesic effect. The similarities in VAS pain scores between the two studied groups could be explained by the usage of PCA for postoperative analgesia. However, the results of the current study supports the previous studies done by Habib *et al*., (2008) and Hong *et al*., (2008), in which they suggested that, transdermal nicotine may be a useful adjuvant to parenteral opioid analgesics in the postoperative period. Another study done by Turan and colleagues (2008), disagreed with the present results. These discrepancies between results could be explained by differences in methodology between studies. Turan *et al*., used high dose perioperative nicotine patch (21mg) for 3 successive days in smokers patients, which may lead to development of tolerance to the centrally mediated analgesic effect of the drug.

Although, nicotine has the potential to increase heart rate and blood pressure because it activates autonomic as well as central cholinergic receptors (Winniford, 1990). The current study did not show any significant difference in perioperative heart rate or blood pressure measurements with transdermal nicotine application versus placebo treatments. These results coincides with previous studies in which the authors hypothesized that autonomic stimulation may have been offset by the fact that patients treated with nicotine were in less pain than those treated with placebo (Flood and Daniel, 2004; Habib *et al*., 2008; Hong *et al*., 2008; Turan *et al*., 2008).

Greenland *et al*. (1998) suggested that, nausea is one of the adverse effects associated with acute nicotine exposure in some sitting. In the present research, although there was a trend towards a lower incidence of postoperative nausea and less rescue antiemetic consumptions in the nicotine group, these differences did not achieve statistical significance. This lower incidence may be explained by the usage of small dose of nicotine patch (7mg), which is known to be tolerated by non-smokers without producing nausea, in addition to the reduction in morphine consumption with associated decrease of opioid related adverse effects. The query antiemetic effect of nicotine observed in this study is in accordance with Ionescu *et al*. (2007) who stated that, the use of a nicotine patch may reduce the incidence of PONV after laparoscopic cholecystectomy and explained the antiemetic effect of nicotine patch by the nicotine inhibition of serotonin 5-HT_3 receptors (Breitinger *et al*., 2001).

The most serious side-effect of postoperative opioid use is respiratory depression (Taylor *et al*., 2005). In the current study, the incidence of postoperative respiratory depression and itching were significantly lower in the nicotine group versus control group. These results can be explained by significantly lower cumulative morphine consumption in the nicotine group than the control group in the first 24 hours after surgery.

As regards the patient satisfaction, the higher response shown in the present study in nicotine group versus control group was marginally significant. Larger sample size may be needed in the future to diagnose the proper significant differences in patients' satisfaction.

In Conclusion: Pre-emptive application of 7mg transdermal nicotine patch, 2 hours before surgery, provided significant reduction of intra- and post-operative analgesic requirements associated with fewer morphine related side effects and better patient satisfaction in non-smoker patients undergoing lumber disc surgery. However, it did not affect the anaesthetic requirement or the perioperative haemodynamics.

Further studies are required to determine the effect of transdermal nicotine application on intra- and post-operative plasma stress hormones levels. The optimum transdermal nicotine dose required for smokers, to control their postoperative pain is also needed to be studied.

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