Egyptian Journal of Anaesthesia (2016) **32**, 299–307

HOSTED BY

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Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

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Research Article

Comparative study between transdermal nicotine and melatonin patches on postoperative pain relief after laparoscopic cholecystectomy, a double-blind, placebo-controlled trial

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Received 1 February 2016; revised 28 April 2016; accepted 9 May 2016
Available online 6 June 2016

KEYWORDS

Transdermal nicotine;
Transdermal melatonin;
Postoperative pain;
Laparoscopic cholecystectomy

Abstract *Background:* This study evaluated the efficacy of transdermal nicotine (TDN) delivery system (15 mg/16 h) or transdermal melatonin (TDM) delivery system (7 mg) 2 h preoperatively for acute postoperative pain after laparoscopic cholecystectomy compared to placebo group (C).
Methods: Sixty female non-smoker patients, aged 18–50 years and ASA I and II undergoing elective laparoscopic cholecystectomy under general anesthesia were included in this randomized controlled double-blind study. Patients were randomly divided into 3 groups 20 each, and C group patients received transdermal placebo patch, TDN group (15 mg/16 h) and TDM group (7 mg/8 h). Assessment of postoperative pain, sedation, hemodynamic variables such as HR and MAP, postoperative monitoring of arterial SpO_2 and side effects (e.g. nausea, vomiting, pruritus, respiratory depression and hemodynamic instability) were done 30 min, 1, 2, 6 and 12 h postoperatively. Postoperative Patient's and Surgeons' satisfaction, Intraoperative bleeding and plasma cortisol (μg/dl) 2 h postoperatively were also assessed.
Results: There was a significant reduction in the VAS score, total pethidine requirements (mg) and significantly higher patient's satisfaction in TDN and TDM groups when compared with the C group postoperatively. The sedation score and surgeons' satisfaction were significantly higher associated with a significant decrease in MAP and Intraoperative bleeding in TDM group compared to C and TDN groups postoperatively. Significant nausea and vomiting in TDN group and significant sedation in TDM group were recorded.
Conclusion: The use of preoperative TDN (15 mg/16 h) or TDM (7 mg/8 h) was an effective and a safe adjuvant for acute pain after surgery.

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Peer review under responsibility of Egyptian Society of Anesthesiologists.

http://dx.doi.org/10.1016/j.egja.2016.05.002

1. Introduction

Intraoperative and postoperative noxious inputs may cause central sensitization, but analgesic interventions given before the noxious stimulus may attenuate or block sensitization [1]. Preventing the establishment of altered central processing by analgesic treatment may result in short-term (e.g., reduction in postoperative pain and accelerated recovery) and long-term (e.g., reduction in chronic pain and improvement in health related quality of life) benefits during a patient's convalescence [2]. Early postoperative pain is the most common complaint after elective laparoscopic cholecystectomy. In 17–41% of the patients, pain is the main reason for overnight hospital stay after day case surgery [3]. Intense acute pain after laparoscopic cholecystectomy might predict the development of chronic pain (e.g. post-laparoscopic cholecystectomy syndrome) [4]. These concepts suggested a possible study design; effective analgesia starts before incision and covers both the period of surgery and the postoperative period.

Transdermal drug delivery offers the potential benefits of simplicity, efficacy and patient acceptance. In theory, a transdermal delivery system can provide a stable serum concentration for an extended period of time with acceptable interpatients' variability [5].

Nicotine, a potent stimulant found in cigarette smoke, was found to have analgesic properties [6]. Nicotine acts on nicotinic cholinergic receptors, which are found in the central nervous system, autonomic ganglia, the neuromuscular junction, as well as in several non-neuronal tissues [7]. Nicotine reduced nociceptive input to the superficial and deep dorsal horn and provides support for α4β2 and α7 nicotinic-mediated antinociceptive actions [8]. Nicotine acts on nAChRs in both the brain and the spinal cord to activate spinal cord descending inhibitory pain pathways [7]. Nicotine-mediated analgesia is thought to involve, at least in part, local release of norepinephrine, with activation of α2-adrenergic receptors [9]. 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 [10]. Nicotine may also produce analgesia by release of endogenous opioids [11]. Furthermore, nicotine has anti-inflammatory actions that could reduce pain [12,13]. Smokers would not experience pain relief from nicotine because of chronic exposure to nicotine and receptor inactivation [14]. Only full-strength nicotine patches (15 mg/16 h or 21 mg/24 h) are subsidized on the Pharmaceutical Benefits Scheme (PBS) [15].

Melatonin (*N*-acetyl-5-methoxytryptamine, MT) is a hormone secreted primarily by the pineal gland in a circadian fashion. The synthesis and secretion of MT are induced by darkness and suppressed by light through retinal nerve fibers projecting to the suprachiasmatic nucleus of hypothalamus, then to the superior cervical ganglion and finally to the pineal gland. During the night, the mean endogenous plasma concentration of MT is ~50–70 pg/mL (216–302 pmol/L) in young adults. In daylight hours, the mean MT plasma concentration is typically < 10 pg/mL (43 pmol/L). Plasma MT levels begin to increase at ~2100 h, peak between 0200 and 0400 h, and return to baseline at 0700–0900 h [16]. MT has a short plasma elimination half-life, ~45 min and when administered orally, shows low and variable bioavailability due to extensive first-pass metabolism and/or variable absorption [17]. Transdermal delivery system for melatonin (TDM) results in sustained plasma MT levels that can be tailored to the normal physiological range and avoid the first-pass metabolism. TDM is intended to be worn for 8 h [18]. Melatonin has sedative, anxiolytic, analgesic, antihypertensive, anti-inflammatory, chronobiotic and oncostatic effects and potent antioxidant properties [19]. Melatonin exerts its analgesic effects through augmentation of $GABA^{-}$ergic systems and morphine anti-nociception, enhancing $GABA^{-}$induced currents and inhibiting glycine effects [20]. Melatonin may enhance the levels of β^{-}endorphins and the anti-nociception induced by delta opioid receptor agonists and could activate MT2 melatonin receptors in the dorsal horn of the spinal cord [21,22]. The long-lasting analgesia induced by melatonin can be blocked by naloxone suggests that opioid receptors are involved in actions of melatonin [23].

The stress response to surgery is characterized by increased secretion of pituitary hormones and activation of the sympathetic nervous system. The changes in the pituitary secretions have secondary effects on hormone secretion from target organs (increased secretion of cortisol from the adrenal cortex) [24].

In this randomized, double-blind, placebo-controlled study, our primary objective was to compare the TDN patches to TDM patches for relieving postoperative pain after laparoscopic cholecystectomy under general anesthesia to detect a mean difference of total analgesic (pethidine) consumption. And our secondary goal was to compare the effects of TDN patches to TDM patches on prolongation of first analgesic requirement time, pain score, sedation score, stress response, patient satisfactory score, surgeon satisfactory score, postoperative monitoring of heart rate, mean arterial blood pressure, arterial SpO_2 and side effects (e.g. nausea, vomiting, pruritus, respiratory depression and hemodynamic instability).

2. Methods

This study was designed to be a randomized, placebo-controlled, double-blind parallel study in which the patients, investigators, anesthesiologists and the surgeons were blinded to the given treatment. This study was conducted in Ain-Shams university hospitals, from April 2013 to July 2015, on 60 female non-smoker patients aged between 18 and 50 years old of ASA physical status I and II of 70–90 kg body weight and height 160–180 cm undergoing elective laparoscopic cholecystectomy under general anesthesia. The study protocol was approved from the institutional ethical committee and written informed consent was obtained from all the patients (see Table 1).

Patients with impaired kidney or liver functions, history of cardiac or central nervous system disease, history of smoking, history of drug or alcohol abuse, history of chronic pain or daily intake of analgesics, uncontrolled medical disease (diabetes mellitus and hypertension), history of intake of non-steroidal anti-inflammatory drugs or opioids within 24 h before surgery or allergy to the used medications, coagulation defect, local infection at the site of application of transdermal patch, patient refusal or duration of surgery more than 120 min were excluded from the study.

Patients were randomly divided into 3 groups, C group (n = 20) each patient received transdermal placebo patch,