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Comment on Nicotine for Postoperative Pain Relief

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Abstract

Whether nicotine could be utilized as an analgesic in the perioperative setting has been the focus of small studies over the past decade. This short communication briefly discusses findings of these small studies. Analgesic properties of nicotine may be influenced by whether the patient is a smoker/ex-smoker or non-smoker, and may also be influenced by gender. The ideal dose when it comes to analgesia is still unknown. Meta-analyses conclude that there is an effect, but it is small, and may be offset by an increased incidence of nausea.

Keywords: Nicotine as an adjunct; Postoperative pain relief

Nicotine for Postoperative Pain Relief

Flood & Daniel [1] in 2004 were the first to test the hypothesis, that nicotine given intraoperatively could have a postoperative analgesic effect. This prompted an article in the Danish journal Ugeskrift for Læger in 2012 [2]. The purpose of this short paper is to describe the evidence regarding nicotine as an analgesic in the postoperative setting, by summing up the findings from the 2012 article, supplemented with new research published since.

Following Flood & Daniel [1] eight other RCTs exploring the analgesic effect of nicotine have seen the light of day [3-10]. Seven of these nine RCTs were included in the Danish 2012 article (PubMed/MEDLINE and EMBASE search completed beginning of June 2016) [1,4-9]. Cheng et al.'s study from 2008 [3] was not included in the 2012 Danish article, because the primary objective here was to test whether anesthesia method affected postoperative pain, but is included here.

It is beyond the scope of this short communication to describe the results of the nine different studies in detail. Instead the major findings have been collected in Tables 1 and 2, which illustrates the methodological differences and the analgesic effect of nicotine either on pain scores, opioid consumption or both, respectively.

RCT	N	Gender	Type of surgery	Smoking status	Nicotine			Antiemetic prophylaxis
					Administration type	Dose (mg)	Exposure (h)	
Flood & Daniel [1]	20	Females	Uterine	Non-smokers	Nasal spray	3	Single dose	Dolasetron 12,5 mg
Cheng et al. [3]	80	Females	Uterine	Non-smokers	Nasal spray	3	Single dose	Dolasetron 12,5 mg
Habib et al. [4]	90	Males	Prostatectomy	Non-smokers	Patch	7	24	Ondansetron 4 mg
Hong et al. [5]	40	Both	Pelvic or abdominal	Non-smokers	Patch	0, 5, 10 or 15	16	None
Turan et al. [6]	85	Females	Uterine	Both	Patch	21, appl. x 3 = 63 total	72	None
Olson et al. [7]	28	Both	Pelvic or abdominal	Smokers	Patch	0, 5, 10 or 15	16	Ondansetron 4 mg
Yagoubian et al. [8]	20	Both	Dental, molar	Unknown	Nasal Spray	3	Single dose	None
Jankowski et al. [9]	179	Females	Uterine	Non-smokers	Nasal spray	3	Single dose	None
Weingarten et al. [10]	89	Females	Bariatric	Non-smokers	Nasal spray	3	Single dose	Scopolamine patch Droperidol 0,625 mg Dexamethasone 4 mg Ondasetron 4 mg

RCT: Randomized Controlled Trial; mg: Milligrams; h: Hours; appl.: Applied; The table is based on tables in the article by Vibe Nielsen et al. [2] and supplemented with results from studies published later.

Table 1: Methodological differences.

Several methodological factors may influence the effect of nicotine, and offer possible explanations to mixed results found so far.

First is whether the patient is a current-, ex- or non-smoker. The hypothesis, that nicotine could have an analgesic effect, stems from observations decades ago, that tobacco smoking increases pain threshold and pain tolerance, which has been attributed to the nicotine content [11]. The mechanism by which nicotine exerts this analgesic effect has not been fully established. It seems to involve inhibitory mechanisms via nicotinic cholinergic receptors (nAChRs) in the central and peripheral nervous system [11,12]. Chronic exposure to nicotine results in changes in receptor number and function, as well as desensitization [11-13]. These factors taken into account it seems likely, that smoking status of a patient may influence the analgesic effect of nicotine. The only study comparing smokers and non-smokers were Turan et al., and only in a subgroup analysis. They found no analgesic effect of nicotine overall, and no difference when analyzing smokers vs. non-smokers. However, the study was not powered for the subgroup analysis [6]. The meta-analysis by Mishriky et al. found, that the opioid sparing effect was limited to non-smokers [14]. Considering the known changes in neurochemistry in smoking individuals, it seems likely that other changes occur over time after smoking cessation. So defining the terms 'non-smoker' and 'ex-smoker' is an entirely different issue - one that has not been considered in any of the studies mentioned, and which may affect the analgesic properties of nicotine.

Secondly there is the matter of gender differences. Research suggests that ovarian hormones underlie gender differences in smoking related behavior [15], suggesting gender differences in responses to nicotine. Further more women metabolize nicotine faster than men [16]. There is also research that supports the theory, that pain response after exposure to nicotine is affected by gender. Jamner et al. found that nicotine increased pain threshold in men but not in women [17]. Also, a recent meta-analysis by Ditre et al. also found that "pain threshold effects were more robust among samples that included more men than women" [18]. Only three [5,7,8] out of nine studies included both men and women, and none of these have explored whether this affected the outcomes.

Thirdly there is considerable variation in nicotine dosage and administration. Only three of the nine studies have examined dose-response effect: Hong et al. found maximum analgesic effect at 5 mg administered as a transdermal patch (as opposed to 10- or 15 mg) [5]. Olson et al. found no effect regardless of dosage [7]. Habib et al. were the only ones to measure plasma nicotine concentrations (measured at 4 and 24 hours postoperatively), and found a significant negative relation between plasma nicotine concentration at 24 hours postoperatively and opioid consumption [4]. This suggested a true analgesic effect of nicotine. Turan et al. administered the highest dose of nicotine (63 mg over 72 hours, as transdermal patch) and found no analgesic effect [6], which could be explained by a proposed mechanism of desensitization of receptors at high nicotine concentrations [12]. Weingarten et al. conducted their study on subjects undergoing laparoscopic gastric bypass surgery, and so had mean-body-mass index of approximately 45 kg/m^2 [10]. They administered 3 mg of nicotine as nasal spray, as in the study by Flood and Daniel [1], and their negative results may be due to effective dose never being reached in their patients, due to a larger volume of distribution.

When considering a new treatment modality, one must weigh the benefits against the possible adverse effects. So far there has been no record of serious adverse events, when using nicotine as an analgesic. Dosage and products used in the studies corresponds to over-the-counter products. Notwithstanding, only 4 of the studies included subjects representing ASA-class ≥ 3 [4,6,9,10], in only 3 studies the median age exceeded 50 years of age [4,5,9], and the total number of study subjects across all of the studies, N=631 in the nine studies represented here, may still be too small to make any certain conclusions.

One of the most frequent side effects of nicotine in any form is nausea. In two studies this outcome was not recorded [1,8]. Five of the studies showed no statistically significant difference in incidence of nausea or vomiting [3-7]. However, Habib et al. [4] found a higher maximum nausea score in the nicotine group, and Hong at al. [5] recorded more incidents of nausea with the higher doses of nicotine. The remaining two studies found increased incidence of nausea and/or increased use of rescue antiemetic treatment [9,10]. Methodological differences limit conclusions in this matter as well, as it is well known that women, non-smokers and use of volatile anesthetics are risk factors for postoperative nausea and vomiting [19]. The meta-analyses both concluded that there was increased risk of nausea when using nicotine. Mishriky et al. moreover concluded that the opioid sparing effect of nicotine, which was limited to non-smokers, was offset by the increased incidence of nausea [14]. This most certainly has to be taken into consideration, since in some research patients' rate nausea a worse outcome than pain [20]. None of the meta-analyses included data from Weingarten et al.'s study [10], in which subjects were given antiemetic prophylaxis with either 3 or 4 drugs, and still exhibited a higher incidence of nausea in the nicotine group.

Table 2 highlights the major results of the nine RCTs. A statistically significant analgesic effect was found in a majority of the studies, which was also recognized in meta-analyses by Mishriky et al. [14] in 2014 and Matthews et al. (Cochrane review) [21] in 2016. However, the meta-analyses, independent of each other, deemed the effects small. Mishriky et al. concluded that the opioid sparing effects was 0-9 mg over the first 24 hours [14], while Matthews et al. found no opioid sparing effect, but a reduction in pain score of less than 1 point (on an 11-point numerical rating scale), and therefore "lower than typically considered meaningful" [21]. Also to be considered is that neither of the meta-analyses includes the negative results of Weingarten et al.'s study [10], as this has been published quite recently. As described in the section above and illustrated by Table 1, the meta-analyses also found a high degree of heterogeneity [14,21].

RCT	Effect on Pain Scores	Effect on cumulative opioid consumption	Postoperative nausea and vomiting (PONV)
Flood and Daniel [1]	First hour postop.: Yes 24 hours postop.: Yes	Yes	Not recorded
Cheng et al. [3]	Isoflurane group: No Propofol group: No	Isoflurane group: No Propofol group: No	No difference between groups
Habib et al. [4]	PACU: No 6 h postop.: No 24 h postop.: No	PACU: No 6 h postop.: No 24 h postop.: Yes	No difference in incidence of PONV Maximum nausea-score was higher in the nicotine group
Hong et al. [5]	First h postop.: Yes 5 days postop.: Yes	No	More incidents of nausea with higher doses, but no statistical significance
Turan et al. [6]	No Smokers vs. non-smokers: no difference	No Smokers vs. non-smokers: no difference	No difference
Olson et al. [7]	First h postop.: Yes 5 days postop.: No	No	No difference
Yagoubian et al. [8]	5 days postop.: Yes	No	Not recorded
Jankowski et al. [9]	(Data collection only in PACU) Inpatients: No Outpatients: No	PACU: No 24 h postop. (all patients): Yes 24 h postop.: (inpatients): Yes	24 h postop. (all patients and inpatients as a subgroup): higher incidence of nausea, nausea-score and use of antiemetic rescue treatment
Weingarten et al. [10]	PACU: No Worst NRS: No	PACU: No 24 h after discharge from PACU: No	Higher incidence of antiemetic rescue treatment
PONV: Postoperative Nausea and Vomiting; postop.: Postoperative; PACU: Postoperative Care Unit; h: Hours; cross all of the studies, N = The table is based on tables in the article by Vibe Nielsen et al. [2] and supplemented with results from studies published later.			

Table 2: Effect of nicotine on postoperative pain and PONV. Results are listed without regard to status as primary-or secondary outcome.

Conclusion

There are still many unanswered questions as to which, if any, patients could benefit from perioperative use of nicotine, and at which dose. Larger randomized controlled studies are needed, that take into account smoking status, gender, plasma nicotine measurements and possibly anesthetic technique as well. Evidence so far points to a very limited analgesic effect, and this effect seems limited to non-smokers, who are more prone to nausea than smokers, and thus the effect of nicotine may be outweighed by increased incidence of postoperative nausea. At present it therefore appears that the use of nicotine as an analgesic is limited.

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