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A preliminary study of 24-hour post-cesarean patient controlled analgesia: postoperative pain reports and morphine requests/utilization are greater in abstaining smokers than non-smokers

Authors' Contribution:

- A** Study Design
- B** Data Collection
- C** Statistical Analysis
- D** Data Interpretation
- E** Manuscript Preparation
- F** Literature Search
- G** Funds Collection

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Summary

Background:

Previous clinical studies have not examined the relationship between nicotine abstinence and opioid use for postoperative analgesia. This may be important because tobacco smokers are routinely required to abstain from smoking just before and during acute post-surgical recovery. This study investigated IV morphine self-administration [patient controlled analgesia (PCA)], subjective pain/drug effects and other measures during post-operative (elective Cesarean section) recovery.

Material/Methods:

Seven females, selected to vary in nicotine use [4 non-using controls (CON), 3 users (NIC)], completed the protocol. Gender, time and type of surgery, and pre- and intra-operative medications were controlled. Subject assessments included the McGill Pain Questionnaire and the Profile of Mood States; drug effects were measured using the Addiction Research Center Inventory.

Results:

Mean (M ±SD) 24-hr morphine responding (button-pressing requests) was significantly higher for NIC (M=183±50) than CON (M=38±10). Weight-adjusted morphine use (mg/kg/24 hr) was significantly higher for NIC (M=1.80±0.23) than CON (M=0.64±0.14). Although the groups reported similar pain severity following morphine loading, NIC patients reported significantly greater pain severity than CON patients after 24 hr PCA.

Conclusions:

These preliminary data suggest that a history of nicotine use and/or short-term nicotine abstinence can modulate morphine use and analgesia during post-operative recovery. These procedures provide a model for studying patterns and determinants of analgesic self-administration in medical settings.

key words:

patient controlled analgesia • pain • self-administration • morphine • opiates • tobacco • nicotine abstinence

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BACKGROUND

About 25% of the population of the United States are smokers and cannot smoke while hospitalized. Furthermore, there has been renewed emphasis on assessment and adequate treatment of pain in hospital settings. Therefore, there is a pressing need to understand whether and to what degree cigarette smokers (presumably due to nicotine abstinence during hospital stays) are at increased risk for post-surgical pain. If such a risk were demonstrated, then physicians could use smoking as a marker to address the special analgesic needs of this patient population.

Patient Controlled Analgesia (PCA) is a safe and effective treatment for acute post-surgical pain. PCA allows the patient to self-administer analgesics (typically intravenous opioids) using limited-access schedules under medical supervision. Relative to traditional on-demand treatment (in which the patient must request medical staff to administer the analgesic), PCA is associated with superior analgesia, more rapid recovery, fewer side effects, and greater patient satisfaction. Patient satisfaction using PCA is related to resting pain levels, preoperative distress, and balancing the number of responses needed to obtain pain relief *versus* side effects [1–3].

Previous clinical studies have not examined the relationship between nicotine abstinence and opioid use for post-operative analgesia. This may be important because tobacco smokers are routinely required to abstain from smoking just before and during acute post-surgical recovery. To our knowledge, there are no prospective, controlled clinical studies that have examined whether patients with different nicotine use/abstinence histories differentially self-administer opioids. A retrospective study did show that female smokers use more narcotic post-operatively than did females who never smoked [4]. Tolerance to nicotine-induced analgesia develops during its chronic administration and abstinence from nicotine can increase nociception [5,6].

In the present study, we examined individual differences in IV morphine use (PCA) and analgesia among post-Cesarean section patients who varied in nicotine use [4 controls with no lifetime nicotine use (CON) *vs.* 3 current nicotine users (NIC)]. Salient variables (gender, type and duration of surgery, and pre- and intra-operative medications) were controlled in this study. The hypothesis was that morphine self-administration would be greater among patients with tobacco use histories who were nicotine-abstinent during hospitalization for their surgery. Pain measures were also evaluated to assess whether pain scores increased along with the predicted morphine utilization. Button-pressing responses (recorded by the PCA pump) and morphine use (actual drug deliveries) may be influenced by several factors; however, only nicotine use and abstinence were examined in this study. The post-surgical time course of morphine responding and self-administration was compared with concurrent self-reported pain and mood, observer-rated pain behavior and side effects, vital signs, and psychomotor performance.

MATERIAL AND METHODS

Participants

The local Institutional Review Board approved this study and all participants ($n=10$) gave written informed consent. Women scheduled to undergo elective Cesarean section at the Johns Hopkins Bayview Medical Center were eligible for this study. Exclusion criteria were: emergency Cesarean section, medical contraindication to the proposed anesthetic regimen, and chronic pain. On the day before surgery, patients participated in a standard pre-operative evaluation and a brief structured interview (with MKG) that included demographic information, psychiatric and substance use history and treatment. A urine specimen for toxicology testing was obtained pre-surgically and analyzed using enzyme multiplied immunoassay (EMIT) for the presence of methadone, opiates, cocaine, amphetamines, barbiturates and benzodiazepines. Urine samples were not collected post-surgically. Nursing staff monitored patients (i.e. 24-hr observation) and verified nicotine abstinence.

Treatment protocol

No analgesics or sedatives were used preoperatively, consistent with the prevailing standard of care. All surgeries began between 0830 and 1130. Intra-operatively, patients had a lumbar epidural catheter placed and were administered 2% lidocaine either alone or with 1:200,000 epinephrine at the discretion of the Anesthesia Care Team. If additional sedation or analgesia was needed, midazolam and ketamine were used. No opioids were administered during the operative period. Patients were informed that, during the postoperative recovery period, they would receive an opioid analgesic *via* the PCA device but were not told which drug, dose, or lock-out interval would be used. They also received standardized pre-operative instructions about the use of the PCA device.

Intravenous morphine PCA was initiated post-operatively using a commercially available PCA pump (CR Bard, Inc, Murray Hill, NJ) in the Labor and Delivery suite when the patient first complained of pain. No basal infusions were set so that the dosage would be entirely determined by the patient. PCA was divided into two phases: loading and maintenance. The loading phase consisted of three consecutive 30-min periods. Initially, the bolus was set at 3-mg morphine with a 6-min lock-out (i.e. time-out) interval. If, upon questioning, the patient did not report feeling "comfortable" at the end of the 30-min period, the morphine bolus dose was increased to 4-mg for the next 30-min period and 5-mg for the third 30-min period. Loading was terminated at 90 mins or when the patient reported feeling "comfortable". The maintenance phase ensued upon completion of loading and continued 24-hrs post-loading, with access to 1.5-mg morphine bolus doses on a 6-min lockout schedule. We planned (*a priori*) a rescue analgesia protocol, such that continued pain reports by the patient despite 7 or more boluses received during the previous hour (reviewed by APM or MSH) resulted in a 1-mg increase in bolus size.

Table 1. Mean (\pm SD) morphine requests, morphine use, and pain intensity reports.

Measure	CON (n=4)		NIC (n=3)		F(1,5) and P values	
Loading						
Morphine button presses	6.5	(3.7)	9.0	(7.6)	NS	
Morphine use (total mg)	12.8	(7.5)	15.0	(10.8)	NS	
Weight-adjusted morphine use (mg/kg)	0.16	(0.09)	0.17	(0.18)	NS	
Infusions=Requests	0.71	(0.26)	0.67	(0.28)	NS	
McGill pain intensity, Pre-loading	2.75	(1.26)	4.33	(0.58)	NS	
Post-loading	1.50	(1.00)	1.67	(0.58)	NS	
Maintenance						
Morphine button presses (number during first 24 hr)	37.8	(9.9)	183.0	(49.6)	34.73	(0.002)
Morphine use (total mg during 24 hr)	49.5	(12.6)	136.0	(24.1)	39.12	(0.002)
Weight-adjusted morphine use (mg/kg/24 hr)	0.64	(0.28)	1.80	(0.39)	21.28	(0.006)
Infusions=Requests	0.88	(0.09)	0.51	(0.11)	24.01	(0.005)
McGill pain intensity, 24 hr post-PCA	0.75	(0.50)	2.33	(0.58)	15.17	(0.02)

Measures

Drug responding/use

Two measures were recorded hourly from the infusion pump during the PCA loading and 24-hr maintenance periods. *Drug responding* was defined as the number of bolus requests, regardless of success (i.e. including those during the lockout interval). *Drug use* was the number of successful bolus requests (i.e. morphine infusions), which was examined with and without adjustment for (pre-delivery) body weight. Both measures were available through a printer connected to the PCA pump. A self-administration efficiency index was developed to characterize the effectiveness with which patients responded for morphine. This derived measure (a proportion ranging from 0 to 1) was defined as the total number of bolus infusions divided by the total number of requests (button presses) during the 24-hr PCA maintenance period.

Self-reports

The primary pain report measure was the McGill Pain Questionnaire (MPQ) [7]. Although the MPQ has several factors, only the global pain severity score (0 – no pain, 1 – mild, 2 – discomforting, 3 – distressing, 4 – horrible, 5 – excruciating) was used due to the small sample size (i.e. limited statistical power) and to emphasize clinical significance/utility. The total mood score of the 65-item Profile of Mood States (POMS) was used to assess the bipolar dimension of negative-positive mood [8]. PCA studies that have assessed affect during recovery have found morphine to increase positive mood [9,10]. Drug effects were measured using the Addiction Research Center Inventory (ARCI), which is a 49-item scale that has two factors, euphoria (MBG scale) and sedation (PCAG scale), that were of interest in the present study [11].

Objective clinical signs

Observer-rated signs of pain were grimacing (0 – no, 1 – yes), moaning (0 – no, 1 – yes), out of bed (0 – no, 1 – yes), restless (0 – not at all, 1 – slightly, 2 – moderately, 3 – extremely), and mobile (0 – not at all, 1 – moves in bed, 2 – ambulatory with discomfort, 3 – ambulatory without discomfort). Observer-rated drug side effects were vomiting (0 – no, 1 – yes), scratching (0 – no, 1 – yes), sedated (0 – not at all, 1 – slightly, 2 – moderately, 3 – extremely), and sweaty (0 – not at all, 1 – slightly, 2 – moderately, 3 – extremely). Vital signs measured were oxygen saturation, respiration rate, heart rate, blood pressure, and oral temperature.

Performance

The Digit Symbol Substitution Test (DSST) was used to measure psychomotor performance [12]. The patient attempted to manually transcribe a randomly presented series of nine different symbols that were associated with the numbers 1 to 9 within a period of 90 sec. Following each test, the number of attempted symbol-to-digit transcriptions (speed) and the number correct (accuracy) were scored. This measure has been used in PCA studies to assess potential cognitive-motor impairment [9,13].

Measurement timeline

On the day before surgery (pre-surgery baseline), the POMS, ARCI and DSST were administered. Because these measures were secondary and repeated measurements with these instruments would have interfered with the primary pain measures immediately after surgery, the only other time that POMS, ARCI and DSST data were collected was at 24 hrs after PCA maintenance. After surgery at the first complaint of pain (pre-loading baseline), subjective pain (MPQ) and objective measures (pain behavior, side effects

Table 2. Patient demographics.

Patient	Race	Age	Pre-Surgical Weight (kg)	# Previous C-sections	Group
2	W	21	71.8	1	NIC (1 pack cigs/day × 8 years)
4	W	34	83.6	2	NIC (1.5 packs cigs/day × 20 years)
10	W	26	72.7	1	NIC (1 pack cigs/day × 16 years)
3	W	29	104.5	1	CON
6	B	26	54.5	1	CON
7	W	35	85.5	2	CON
9	B	24	86.4	1	CON

and vital signs) were collected. Immediately after the morphine loading period but before PCA maintenance dosing began (post-loading time point), these same subjective pain, and objective measures were collected. These signs/symptoms were re-assessed at 2 and 4 hrs post-loading to monitor progress. However, to avoid interfering further with clinical care, no additional data were collected until 24 hrs post-loading (all measures above).

Data analysis

Morphine responding and morphine use data during the loading period and the 24-hourly PCA maintenance period were examined graphically using cumulative records. Total 24-hr morphine responding and total 24-hr morphine use were analyzed separately using one-way Group (CON vs. NIC) Analyses of Variance (ANOVAs). All other measures were analyzed using two-way mixed model ANOVAs, with Group as the between subject factor and Time Points (which varied across different measures [see description above]) as the within subject factor. In general, Time-related effects were not significant at 2 hr and 4 hr post-loading (the only exceptions were MPQ global pain severity and objective pain behaviors, which improved for both groups). Therefore, for simplicity, these data are omitted from the text and Table 1, and the focus is on pre- and post-loading and 24 hr post-PCA maintenance results. *T*-tests were conducted to assess group differences in pain severity scores at these time points. All significant effects are $P < 0.05$ unless otherwise indicated.

RESULTS

Patient characteristics

Three patients were excluded from analysis. Patient #1 reported a history of psychiatric problems and past use of several illicit drugs. Patient #5 reported recent depression and cocaine abuse, and patient #8 reported chronic heroin and cocaine abuse and being in methadone maintenance. The recent drug use reports by patients #5 and #8 were confirmed by urine toxicology. The other seven subjects had no illicit drugs/metabolites detected with urine toxicology. The seven female participants who completed the protocol (see Table 2) ranged in age from 21 to 35 years and reported 8 to 12 years of education. All had at least one previous

Cesarean section and all delivered at a gestational age ranging from 38 to 40 weeks without major medical complications. At the time of their previous Cesarean section, all subjects received routine post-operative care including the use of nurse-administered analgesia (opioids) rather than PCA. In the CON group, one patient (#9) had a history of sickle cell anemia and another (#3) had a history of insulin-dependent diabetes mellitus. No patient experienced any labor pain prior to her elective Cesarean section surgery.

Three patients reported using tobacco/nicotine (NIC) daily in the 30 days prior to admission, and all three last smoked on the day of hospital admission. Three of the other four control patients (CON) denied ever having used tobacco/nicotine and the other patient had smoked 1 to 2 cigarettes per day for three years, but stopped one year prior to delivery. Four patients reported occasional moderate alcohol use, but all denied alcohol use during their pregnancy. All patients denied using most illicit drugs (heroin, cocaine, benzodiazepines, barbiturates, hallucinogens and inhalants), although two patients (#2, 6) reported brief experimental use of marijuana only during adolescence. Three CON patients (#3, 7, 10) reported a history of diet pill (amphetamine) use that stopped 2–5 years prior to delivery. Three participants (#3, 4, 10) reported daily caffeine use

Morphine responding/use

Figure 1 shows individual-patient cumulative records for morphine button pressing (upper panel) and consumption (lower panel) during the postoperative recovery period. Table 1 summarizes the group differences on the primary outcome measures. Morphine button pressing and use were significantly higher for NIC patients than CON patients only during the PCA maintenance but not during the loading period (Table 1). This group difference became apparent between 1 and 6 hrs after starting PCA maintenance (Figure 1), at a time that corresponds to about 30 hrs after these NIC patients last smoked cigarettes. When morphine use was adjusted for patients' body-weight, this measure remained significantly higher for the NIC than the CON group (Table 1). The self-administration efficiency index ($\# \text{ boluses} \div \# \text{ requests}$) was significantly higher for the CON than the NIC group; this reflects greater unproductive (i.e. lockout interval) button pressing by NIC than CON patients.

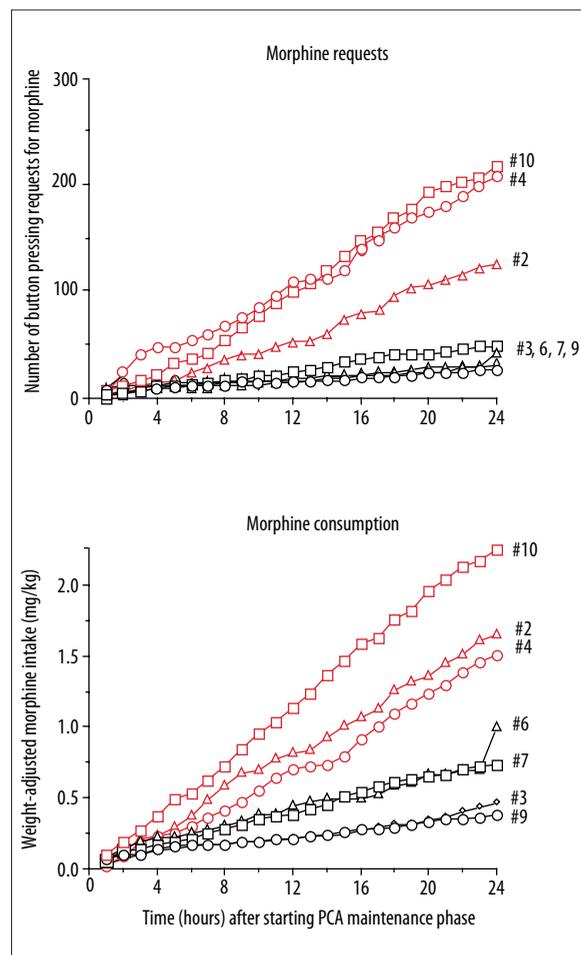


Figure 1. Individual patterns of morphine button pressing behavior (upper panel) and body weight-adjusted morphine consumption (lower panel) during 24-hr PCA. Numbers to the right of each cumulative record indicate the consecutive patient number (see Table 2). Patients #2, #4 and #10 reported current nicotine use (with minimum 24-hr abstinence during hospitalization prior to PCA) and patients #3, #6, #7 and #9 reported no current nicotine use.

Pain symptoms

Prior to loading with morphine, NIC patients reported somewhat higher global pain severity scores on the MPQ (“horrible” to “excruciating” range) than CON patients (“discomforting” to “distressing” range; see Table 1), but this apparent group difference at baseline was not significant. Immediately after the loading period, MPQ pain severity scores decreased to similar levels (“mild discomfort”) in both groups (see Table 1). However, after 24 hrs of PCA maintenance, pain severity was significantly higher for NIC than CON patients (see Table 1).

Objective pain behaviors

All seven participants were observed to grimace prior to the loading period and none grimaced at any time point after loading, indicating improved pain control; although this measure could not be statistically analyzed for lack of between-subject variance at each time point, the clinical sig-

nificance is clear. Observer-rated restlessness (0–3 scale) was greatest prior to loading ($M \pm SD = 0.86 \pm 0.69$), significantly decreased after loading ($M = 0.14 \pm 0.38$), and remained lower at the 24-hr time point ($M = 0.29 \pm 0.49$), with no group (NIC vs. CON) differences. No patient ever showed evidence of moaning as a sign of pain. No patient was out of bed before or after loading. At the 24-hr time point, all 3 NIC patients were out of bed and 2 of the 4 CON patients were out of bed. Participants were rated as being increasingly mobile after surgery; mobility scores (0–3 scale) increased from pre-loading ($M = 0.14 \pm 0.38$) to post-loading ($M = 0.28 \pm 0.49$) to the 24-hr time point ($M = 0.86 \pm 0.69$).

Drug and mood effects

There were no significant increases on any ARCI drug effect or POMS mood scale for either group from the pre-surgery assessment to the 24-hr time point. Thus, at the time points measured, the groups did not differ in subjective mood, euphoria or sedation during PCA access.

Vital signs

There was no evidence of clinically significant respiratory depression (defined as breathing rates ≤ 10 breaths/min and/or oxygen saturation $\leq 92\%$) for any participant nor were there clinically significant changes in other vital signs.

Psychomotor performance

There were no significant changes in the number of DSST symbol-digit translations attempted or number correct for either group during recovery.

DISCUSSION

Historically, medical professionals have not considered the interaction between nicotine use/abstinence and opioid-induced analgesia. Patients with a history of smoking have been reported to use more PCA morphine than non-smokers in retrospective analyses [4,14]. In this prospective study, we observed that post-operative patients with current (≥ 1 pack) daily nicotine use (NIC), but abstaining during hospitalization, demonstrated significantly greater morphine responding and consumption than patients without nicotine use (CON). Although the schedule of drug availability can influence patterns of self-administration, the dosing schedule in this study represents a clinically relevant practice pattern, and no patient used the maximum available amount of morphine.

One potential explanation for the group difference in morphine responding/use is that NIC patients experienced greater pain severity (i.e., were hyperalgesic) from surgery and, thus, self-administered morphine more frequently to achieve analgesia. If so, then greater pain reports would be expected to precede morphine responding. Unfortunately, the present study was not designed to address the cyclic interaction of pain reporting/morphine use; however, NIC patients showed a non-significant tendency to report more pain before loading (this trend was neutralized by morphine loading), and did report significantly greater pain at 24 hr post-PCA. While these data could suggest that the pain experienced by NIC patients was partially unrelieved despite

greater PCA utilization, further research is needed to address this issue.

A second potential explanation for the group difference in morphine responding/use is that NIC patients might have experienced nicotine abstinence symptoms (e.g. negative mood) that prompted greater morphine self-administration. In laboratory animals exposed to nicotine, abstinence enhances nociceptive transmission [5,6]. Further, precipitated nicotine abstinence signs in an animal model can be attenuated by morphine [15,16]. Taken together, this evidence implies that nicotine abstinence may modulate functioning of the endogenous opioid system. Therefore, in the present study, it is possible that NIC patients may have self-administered higher doses of morphine to relieve their nicotine abstinence symptoms. One limitation of this study, however, is that nicotine abstinence symptoms were not directly measured with questionnaires. The POMS data, however, did not support the hypothesis that negative mood was higher in the NIC group. This remains an important issue for understanding the mechanism(s) underlying these group differences in analgesic utilization. Regardless, the increased morphine consumption for the recently nicotine-abstinent patients suggests that clinicians should consider providing this group more liberal access to opioid PCA.

A third possible explanation for the group difference in morphine responding/use might be that NIC patients (due to their habitual drug use and possible neurochemical alterations) sought positive mood change (e.g. euphoria) rather than relief of aversive withdrawal symptoms. Again, however, the POMS data and the ARCI MBG (euphoria) scale did not show that the groups differed in mood. Furthermore, the NIC patients were not more sedated, cognitively impaired, nor were their vital signs altered as a result of their greater morphine consumption. This indicates that a greater clinical allowance for morphine use in NIC patients can be achieved with a sufficient safety margin.

Several factors that might confound the present results were controlled. The individual differences observed here are obviously not gender-related. They are also unlikely to be explained by differences in the extent of surgical incision, pre- or intra-operative anesthetic regimens (which were highly constrained and precluded opioids), labor pain (absent in all cases), medical complications, or diurnal variation (all surgery and recovery periods were on the same schedule). It is possible the groups differed in their comprehension of PCA pump operation and this could account for the observed differences in button pressing behavior. Future studies should test for comprehension to minimize such effects. Factors that limit conclusions from this study include the small sample size and potential bias in the group demographics (although we found no disparities in self-reported psychiatric or drug use histories). Difficulty in achieving comfort during the loading period could discourage patients from utilizing the PCA device during the maintenance period. However, we do not believe this occurred because the groups did not significantly differ in morphine use or McGill pain severity scores during the loading period, yet they differed significantly during the maintenance period. Overall, the ability to control (or minimize the influence of) these factors will increase power to detect statistically significant differences.

One surprising aspect of the results is that robust differences were observed between small groups of patients differing in nicotine use/abstinence. Although these preliminary results must be interpreted cautiously because of the small sample size, they demonstrate the differences between nicotine naive and nicotine-abstaining subjects in their need for narcotic analgesia. Also, this study suggests a methodology that can be used to analyze this behavior in other patient populations.

CONCLUSIONS

The present study establishes that nicotine abstinence results in clinically and statistically different morphine requests/utilization compared to non-smokers. The number of bolus requests as well as the amount of drug (relative to body weight) is a useful measure to assess patient's self-perception of pain. Other assessment procedures in this study – drug effects (e.g. euphoria), graded pain response (e.g. after rest, paced breathing, and coughing), and objective indices of pain behavior (e.g. mobility, restlessness) – provide functional measures of medication effectiveness and recovery that can be helpful to physicians and nurses. The next useful steps should be to (1) determine whether differential PCA response among tobacco using patients is due to their inherently greater pain sensitivity, nicotine withdrawal symptoms (due to abstinence during hospitalization), greater drug-seeking behavior, or some interaction of these factors; and (2) develop a clinical strategy for managing post-operative pain in this patient subgroup.

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