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Effects of Tobacco Smoking On Measures of Cold-Induced Pain

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Abstract

Nicotine's effect on human pain perception is uncertain. This study's purpose was to determine whether pain thresholds, pain tolerances, or ratings of pain intensity differ among smokers (S), non-smokers (NS), and abstaining smokers (AS). Twenty-nine male and female smoking and non-smoking subjects participated. Smokers were randomly assigned to either smoke 1 cigarette 15 minutes prior to testing (S group) or abstain from smoking for 10 hours prior to testing (AS group). Pain was induced by employing the cold pressor test. Pain threshold, pain tolerance, and a rating of pain intensity were measured and compared among groups. Pain threshold was the time from the beginning of the cold pressor test to the subject's report of pain. Pain tolerance was measured from the pain threshold to the subject's voluntary removal of the extremity from the cold pressor test apparatus. Pain intensity was measured using a visual analog scale. Pain tolerance and ratings of pain intensity did not differ among the three groups. The S group had a significantly higher pain threshold ($\bar{x} = 35.51 \pm 19.76$ s) than the NS group ($\bar{x} = 16.32 \pm 8.96$ s) ($p = 0.013$; $\alpha = 0.05$). Nicotine may attenuate the sensation of pain in humans, suggesting that pain management may need to be adjusted for abstaining smokers. Further research is warranted.

Abstract

Nicotine's effect on human pain perception is uncertain. This study's purpose was to determine whether pain thresholds, pain tolerances, or ratings of pain intensity differ among smokers (S), non-smokers (NS), and abstaining smokers (AS). Twenty-nine male and female smoking and non-smoking subjects participated. Smokers were randomly assigned to either smoke 1 cigarette 15 minutes prior to testing (S group) or abstain from smoking for 10 hours prior to testing (AS group). Pain was induced by employing the cold pressor test. Pain threshold, pain tolerance, and a rating of pain intensity were measured and compared among groups. Pain threshold was the time from the beginning of the cold pressor test to the subject's report of pain. Pain tolerance was measured from the pain threshold to the subject's voluntary removal of the extremity from the cold pressor test apparatus. Pain intensity was measured using a visual analog scale. Pain tolerance and ratings of pain intensity did not differ among the three groups. The S group had a significantly higher pain threshold ($\bar{x}$ = 35.51 ± 19.76 s) than the NS group ($\bar{x}$ = 16.32 ± 8.96 s) ($p = 0.013$; $\alpha = 0.05$). Nicotine may attenuate the sensation of pain in humans, suggesting that pain management may need to be adjusted for abstaining smokers. Further research is warranted.

Effects of Tobacco Smoking On Measures of Cold-Induced Pain

Introduction

The antinociceptive effect of nicotine has been recognized since as early as 1921 (Mendenhall, 1921). This effect is an intricate phenomenon that involves a wide range of subtypes of the nicotine receptor based on the pain type and location of action. Antinociception via activation by nicotine on cholinergic pathways in the nervous system has been implicated in pain tests of different species (Aceto, Bagley, Dewey, Fu, & Martin, 1986; Damaj, 2000; Decker, Meyer, & Sullivan, 2001; Hamann & Martin, 1992; Iwamoto, 1991; Marubrio et al., 1999).

The antinociceptive characteristic of nicotine has been examined from a psychological standpoint. The analgesic property of nicotine may serve to reinforce the smoking behavior, causing people to smoke independent of withdrawal symptoms caused by the nicotine present in cigarettes (Pomerleau, Turk, & Fertig, 1984).

Nicotine has been noted to cause an increase in the threshold to painful stimulation. Fertig, Pomerleau, and Sanders (1986) found that individuals who smoked a high nicotine cigarette versus a zero nicotine cigarette had a higher pain threshold. Furthermore, abstaining smokers (smokers who had not smoked for the past 12 hours) were noted to have a higher pain threshold versus minimally deprived smokers (smokers who had not smoked for the last 30 minutes) (Pauli, Rau, Zhaung, Brody, & Birbaumer, 1993). However, there has been no previous study that has addressed the potential differences in measures of pain threshold, tolerance, and intensity between groups of

smokers, abstaining smokers, and non-smokers all in the same study. In addition, the aforementioned studies only evaluated measures of pain in a population of male smokers.

There are two different theories that explain the influence of nicotine on the neuronal nicotine receptors (nAChRs) and its antinociceptive effect. Both stem from the fact that nicotine is able to cross the blood-brain barrier. Nicotine exerts its antinociceptive effects within the central nervous system where nAChRs are found in both the spinal cord and brain. Previous research has suggested that the high-affinity nicotine site in the brain, the $\alpha 4\beta 2$ nAChR subtype, plays an important role in antinociception (Bitner et al., 1998; Damaj et al., 1998; Flores, Rogers, Pabreza, Wolfe, & Kellar, 1992; Marubrio et al., 1999).

One theory of antinociception proposes that nicotine binds to nAChRs, causing ion channels to open and the cell to depolarize. It is theorized that nicotine augments or activates descending pain modulation pathways to produce antinociception. However, a direct injection of a single nicotine antagonist into the spinal cord does not completely block the antinociceptive effect of systemic nicotine; a complete block will only occur with the injection of a combination of nicotine antagonists. Nicotine appears to activate a number of descending pain pathways (Iwamoto & Marion, 1993; Rogers & Iwamoto, 1993). According to the gate control theory, descending pathways act in the spinal cord by modulating the activity of a subset of neurons in the substantia gelatinosa. The substantia gelatinosa is the location of a proposed "gate" within the spinal cord where pain fibers from the periphery converge. In order for pain to be recognized by the brain, summation must be strong enough to overcome both the gate and the descending

pathways that help keep the gate closed (Melzak & Wall, 1965). Nicotine, by activating descending pathways, requires a higher pain threshold to be reached before pain transmission is permitted (Damaj, Meyer, & Martin, 2000; Marubrio et al., 1999; Rao, Correa, Reid, & Lloyd, 1996).

A second theory proposes that nicotine exerts its antinociceptive effects by interacting with the endogenous opioid system. The administration of nicotine has been noted to cause the release of endogenous opioids, *in vivo* and *in vitro*, in both animals and humans (Houdi, Pierzchala, Marson, Palkovits, & Van Loon, 1991; Pierzchala, Houdi, & Van Loon, 1987; Pomerleau, Fertig, Everett-Seyler, & Jaffe, 1983; Suh, Song, Choi, Chung, & Kim, 1996). Furthermore, the abrupt cessation of the consumption of nicotine results in significantly lower levels of β-endorphin within a 24-hour period. This finding suggests that acute nicotine abstinence may be associated with decreased levels of endogenous opioids, thus resulting in a decrease in pain threshold (Rosencrans, Hendry, & Hong, 1985).

The two endogenous opioids influenced by nicotine are enkephalin and β-endorphin (Houdi et al., 1991; Krishnan-Sarin, Rosen, & O'Malley, 1999; Suh et al., 1996). Within the spinal cord, enkephalin can bind to δ receptors present on nerve terminals that contain stimulatory neurotransmitters. These opioid-bound nerve terminals, in turn, are less likely to release the neurotransmitters involved in pain transmission.

Hollt and Horn (1991) found that nicotine leads to the release of β-endorphin and increases the messenger RNA necessary for the production of its precursor. They also found that β-endorphins inhibit the neurotransmitters involved in sensory transmission

via pain pathways. The release of the two aforementioned endogenous opioids and their effect on neurotransmitters negatively influence the transmission of the pain impulse. As a result, a stronger impulse is required to surpass the threshold necessary for pain perception to occur. This leads to a reduction in the physical and emotional impact of pain.

The objective of this study was to examine the effects of tobacco smoking on perception of pain elicited by the cold pressor test (CPT) (Chen, Dworkin, Haug, & Gehrig, 1989; Wolf & Hardy, 1941). Our null hypothesis was that there would be no difference in pain thresholds, pain tolerances, or ratings of pain intensity among smokers, acutely abstaining smokers, and non-smokers. An understanding of nicotine's role in pain perception would allow a healthcare provider to tailor the administration of pain medication to an individual based on smoking status. Knowledge of the relationship between nicotine and pain could also be used to optimize an individual's attempt at smoking cessation.

Methods

Institutional review board approval from Brooke Army Medical Center at Fort Sam Houston, Texas was obtained prior to the recruitment of subjects. A convenience sample of 29 active duty military members and dependents between 22 and 48 years of age were enrolled for this study (15 males, 14 females). Subjects were recruited primarily from the students, faculty, and family members of personnel at the U.S. Army Medical Department Center and School at Fort Sam Houston, Texas. Twenty-one of the subjects

met criteria for non-smokers. Of the remaining 8 subjects, 3 were randomly assigned as smokers and 5 were randomly assigned as abstaining smokers.

Inclusion criteria required subjects to be 18-50 years of age, eligible for Department of Defense health care benefits, and able to speak, read, and comprehend the English language. Exclusion criteria eliminated the participation of subjects diagnosed with any of the following conditions: hypertension defined as a blood pressure greater than 130/85 mm Hg (American Heart Association, 2003), coronary artery disease, diabetes, cold hypersensitivity (Goldberg & Pittman, 1959), rheumatoid conditions, vasospastic disease, numbness or unusual sensations in the hands, a history of nerve damage, serious burn or frostbite in the non-dominant upper extremity, or chronic pain. Also, the regular use of prescribed or over-the-counter pain medications, smokeless tobacco, a nicotine patch, or nicotine gum resulted in exclusion of a potential subject from participation in this study.

Informed consent was obtained after the subject read through a consent form and had an opportunity to ask questions. An ombudsman was utilized during the consent of enlisted active duty personnel in order to avoid the appearance of coercion. Each subject completed a short questionnaire covering subject demographics, health history, and medication use. A table of random numbers was used to assign subjects identified as smokers to one of two treatment groups: smokers or abstainers. Based upon random assignment of smoking status, subjects were given either a smoking or abstaining protocol to follow prior to their participation in the CPT.

Smoking status had three levels. A smoker was a subject who reported that they smoked cigarettes on a daily basis. An abstaining smoker was a subject defined as a smoker but asked to abstain from smoking for 10 hours prior to administration of the cold pressor test. A non-smoker was a subject who had never smoked or had quit smoking for at least 1 year and was not currently using any other type of nicotine product. Gender had two levels: male and female.

The dependent variables were pain threshold, pain tolerance, and pain intensity. Pain threshold was the amount of time elapsed from the moment the subject's hand was placed into the CPT apparatus until the subject first reported the sensation of pain. Pain tolerance was the amount of time elapsed until the subject determined the pain was unbearable and removed the hand from the CPT apparatus. Pain intensity was measured on a horizontal 100 mm visual analog scale (VAS) anchored on the left with the words "no pain" and anchored on the right with the words "worst pain imaginable." Pain intensity was marked by the subject upon removal of the hand from the CPT apparatus. Reliability of the one-dimensional VAS has been supported by test-retest measurements (Gaston-Johansson, Fridh, & Turner-Norvell, 1988; Harms-Ringdahl et al., 1986; Revill, Robinson, Rosen, & Hogg, 1976; Seymour, 1982), and its validity has been supported with strongly positive correlation scores when compared with simple descriptive pain scales (Choiniere & Amsel, 1996; Ohnhaus & Adler, 1975; Woodforde & Merskey, 1972).

Smokers followed a smoking protocol. They were given 5 minutes to smoke one cigarette of their own brand. All smokers were required to smoke their cigarette down to

the level of the filter. Fifteen minutes after finishing the cigarette, the subject participated in the CPT. Abstainers followed a separate protocol. They were instructed to stop smoking 10 hours prior to their scheduled participation in the CPT.

Instructions were read from a standard script, to each subject, by the same investigator. This script explained that, on the investigator's cue, the subject was to insert the non-dominant hand (up to the distal wrist crease) into the CPT apparatus. This apparatus consisted of an insulated plastic tank containing a slurry of crushed ice and water maintained at1 °C ± 1 °C. Subjects were instructed to verbally state the word "pain" aloud when the sensation of cold changed to a sensation of pain. Using a digital stopwatch with split time capabilities, this time was noted as pain threshold. The subject was further instructed to remove their hand from the CPT apparatus when the pain had become unbearable. Using the same digital stopwatch, this time was noted as pain tolerance. Immediately upon removal of the hand from the CPT apparatus, the subject was asked to indicate a rating of pain intensity by making a mark on a visual analog scale (VAS). The VAS and a fine point pen were located on a table in front of the subject.

The CPT apparatus was located on the subject's non-dominant side. It was positioned at a level that would not place undue strain on the extremity or torso when the subject's hand was submerged to the distal wrist crease. To minimize measurement error, the same researcher accomplished all of the data collection (Levine & De Simone, 1991). This researcher was blinded as to whether the subject was a non-smoker, smoker, or abstaining smoker, and was the only researcher in the room while the subject was participating in the CPT.

A certified thermometer (ERTCO Precision, West Patterson, NJ) was used for determination of ice water bath temperature prior to the testing of each subject. This thermometer was factory certified against National Institute of Standards and Technology certified thermometers. At 0 °C, the thermometer was factory corrected to within ± 0.1 °C.

A digital stopwatch (Model 226, Sportline INC., Campbell, CA) was used to measure time to pain threshold and tolerance. This stopwatch was measured against the atomic clock signal at the Naval Observatory in Washington for reliability. The mean difference was -0.1 seconds.

This was a prospective, quasi-experimental study using a 2 × 3 factorial design for two independent variables (smoking status and gender), and three dependent variables (pain threshold, pain tolerance, and pain intensity). The data were analyzed using the SPSS 11.0 statistical package. Separate ANOVA's were used to analyze pain threshold, pain tolerance, and pain intensity. The between groups comparison was accomplished using a one-way ANOVA for each dependent variable. Tukey's HSD was then utilized to accomplish a *post hoc* analysis and identify where significant differences between groups existed. An alpha level of 0.05 was utilized for the purposes of this study.

Results

As shown in Table 1, a significant difference was found between groups in pain threshold ($F = 5.674, p = 0.009$). *<Insert Table 1 about here>* A *post hoc* analysis of pain threshold showed a significant difference between smokers and non-smokers with a mean difference of 19.19 seconds (see Table 2). The smoking group was noted to have a

significantly higher pain threshold ($\bar{x}$ = 35.51 ± 19.76 s) than the non-smoking group ($\bar{x}$ = 16.32 ± 8.96 s) ($p = 0.013$; $\alpha = 0.05$). *<Insert Table 2 about here>*

Pain tolerance and ratings of pain intensity did not differ among the three groups ($p = 0.066$ and $p = 0.314$, respectively) We were unable to analyze for variations in pain threshold, pain tolerance, or pain intensity based on gender due to an inadequate sample size and inequality between group sizes. We were able to reject the null hypothesis that there would be no difference in pain thresholds between the three groups, but we were unable to reject the null hypothesis with regards to pain tolerance or pain intensity.

Discussion

The primary purpose of this study was to determine whether or not nicotine consumed via a cigarette would alter the pain threshold, pain tolerance, or perception of pain intensity in smokers versus non-smokers using the CPT. The secondary purpose was to determine if a difference in these same pain measurements existed between smokers instructed to smoke 15 minutes prior to the CPT and those smokers asked to abstain from smoking for 10 hours (Benowitz, Jacob, Jones, & Rosenberg, 1982) prior to the same test. Since nicotine levels do not differ significantly from one brand of cigarette to another (U.S. Department of Health and Human Services, 1988), the nicotine dose delivered to each smoking subject was considered to be controlled.

The results of this study suggest that nicotine acutely raises the pain threshold for smokers (see Figure 1). We speculate that the noted increase in pain threshold is the result of nicotine's augmentation of the descending pain pathways, which modulate the "gate" (Melzak & Wall, 1965) located in the substantia gelatinosa of the dorsal horn of

the spinal cord. As a result, a higher pain threshold must be reached before pain transmission to the brain is permitted. This is consistent with other studies suggesting that nicotine enhances descending pain pathways (Damaj et al., 2000; Marubrio et al., 1999; Rao et al., 1996). Nicotine uptake into the central nervous system occurs within approximately two minutes of smoking a cigarette. Nicotine's elimination half-life is two hours (U.S. Department of Health and Human Services, 1988). We suspect that the abstaining smokers lost nicotine's beneficial analgesic effects during the CPT because ten hours had elapsed since their last cigarette.

Previous studies have concluded that endogenous opioids are released in response to nicotine administration (Houdi et al., 1991; Pierzchala et al., 1987; Pomerleau et al., 1983; Suh et al., 1996). It has also been noted that an abrupt cessation of the consumption of nicotine results in significantly lower levels of β-endorphin within a 24-hour period (Rosencrans et al., 1985). Consistent with these findings, we conclude that a diminished level of endogenous opioids may have resulted in the apparent, but insignificant, decrease in pain threshold noted in the abstaining group when compared to the pain threshold noted in the smoking group. The results of this study also suggest that the increase in pain threshold may no longer exist in the abstaining smoker.

While there was no significant difference in pain tolerance between the groups, the trend is consistent with those noted in pain threshold (see Figure 1). Smokers appeared to have an increase in pain tolerance as compared to the other two groups. We suspect that had a larger sample of smokers and abstainers been obtained, a significant difference in pain tolerance between groups may have been noted. *Post hoc* power

analysis of the number of subjects we obtained is 0.43. Thus, it is likely that this power was too low to find significant differences between groups even if they existed. <*Insert Figure 1 about here*>

There were no significant differences in pain intensity. This may be explained, in part, because our subjects were recruited from a convenience sample of primarily active duty military personnel: a culture in which the admission of pain may be associated with weakness. Therefore, we may not have received an accurate rating of pain intensity on the VAS. It should be noted, however, that smokers had lower ratings of pain intensity compared to nonsmokers and abstaining smokers.

Nicotine's effect on pain perception in humans is uncertain. Previous research suggests the acute use of nicotine seems to reduce the perception of pain in humans. Fertig et al. (1986) found that their smoking subjects had an increase in pain threshold when subjects smoked a high-yield versus sham cigarette. Nesbitt (1973) noted that smokers had a higher pain endurance threshold than non-smokers when both groups smoked a high nicotine cigarette. Pauli et al. (1993) determined that deprived smokers had a higher pain threshold versus minimally deprived smokers. Perkins et al. (1994) found that individuals given nicotine via nasal spray had decreased pain sensitivity regardless of smoking status. Pomerleau et al. (1984) found that smokers had a higher pain threshold when subjects smoked their usual cigarettes versus sham cigarettes. Silverstein (1982) noted that smokers who smoked a high nicotine cigarette had a higher pain threshold versus non-smokers. Our results are consistent with these previous

research findings since the pain threshold of smokers in this study was found to be significantly greater than non-smokers.

However, Shiffman and Jarvik (1984) found smoking had no effect on pain threshold in smokers who smoked a high nicotine versus sham cigarette. Sult and Moss (1986) noted no effect of smoking on ratings of pain in smokers who smoked a moderate nicotine versus sham cigarette. Knott (1990) found no difference in pain ratings in smokers who smoked their own cigarette versus when they abstained from smoking. Unlike the studies that support the existence of nicotine's analgesic properties in humans, the populations examined in these three studies consisted almost entirely of females. This suggests that gender differences may exist in how nicotine influences pain perception, as suggested by Jamner, Girdler, Shapiro, and Jarvik (1998). We included male and female subjects in our study in order to determine if gender differences exist, but were unable to analyze for these differences because our sample size was inadequate.

Our study involved the evaluation of pain produced by the CPT. This test reliably and validly produces pain most similar to the pain experienced in the clinical setting (Chen et al., 1989; Wolf & Hardy, 1941). The CPT is an experimental tonic pain model that simulates clinical pain more effectively than electrical, thermal, or ischemic pain (Chen et al.). It is able to measure the evolution of pain sensation as it maintains an unchanging stimulus level, unlike previously mentioned tests (Blasco & Bayes, 1988). The CPT produces a severe pain that increases quickly and is tolerated for a much shorter time (Gracely, 1989). The pain produced by the CPT is routinely used in assessing analgesic properties of medication since it is sensitive to pharmacologic modulation

(Chen et al.). Since the CPT is a low risk test that does not result in any permanent damage to test subjects, it was used to evaluate pain threshold and pain tolerance of our test subjects (Walsh, Schoenfeld, Ramamurthy, & Hoffman, 1989). No instances of cold-hypersensitivity, the most common side-effect of the CPT, were noted in any of the subjects that participated in this research study.

Further scrutiny of the effects of nicotine on measures of pain between smokers and abstaining smokers is warranted. Smokers are often forced to become abstainers during a hospitalization. Our study suggests that the presence of nicotine raises the pain threshold, and that acute cessation of nicotine consumption may result in a lowered pain threshold and tolerance in the abstaining smoker. As a result, the abstaining smoker patient population may require more pain medication in the perioperative period compared to nonsmokers. If health care providers are made aware of the potential influences that nicotine has on pain perception, then pain medication regimens could be tailored to a patient's smoking status.

Further research may also aid in the development of more successful smoking cessation programs. It has been suggested that physiological changes after nicotine consumption may result in direct activation of pain pathways (Damaj et al., 2000; Marubrio et al., 1999; Rao et al., 1996) or endogenous opioid release (Houdi et al., 1991; Pierzchala et al., 1987; Pomerleau et al., 1983; Suh et al., 1996). This may reinforce the smoking behavior by relieving some subconscious pain sensation in the absence of nicotine withdrawal symptoms (Pomerleau et al., 1984). As such, by prescribing an

analgesic, it may be possible to make an individual's attempt at smoking cessation more successful.

There are limitations associated with this research study. We were unable to obtain our *n* due to time constraints. In addition, the military training environment from which we were recruiting subjects highly discouraged its trainees from smoking. We suspect that, had we achieved our *n*, there would have been a significant difference in pain tolerance between the smokers and non-smokers.

Group sizes were also unequal. This inequality may have resulted in the significantly higher pain threshold noted between the smoking and non-smoking groups. Furthermore, we were unable to analyze for the different within group effects that nicotine may have on pain measurements based on gender.

Finally, the inclusion criteria for this study called for healthy subjects between 18-50 years of age. According to the Society of Interventional Radiology (2003), evidence of peripheral vascular disease is not significant until after age 60. In order to prevent this variable from interfering with our results, 50 years of age was chosen as the upper limit for age. This may limit the generalizability of our results to other subject populations.

In summary, the results of this research study suggest that nicotine attenuates the sensation of pain in humans. Pain management modalities may need to be adjusted for smokers during the perioperative period, when they are unable to smoke cigarettes. Additional research that evaluates the effects of nicotine on pain perception among male and female populations is needed. In addition, attaining a larger sample size of smokers

and abstaining smokers might reveal further significant differences in pain measurements between these groups.

Disclaimer

The views expressed in this material are those of the authors, and do not reflect the official policy or position of the U.S. Government, the Department of Defense, or the Department of the Air Force. The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32CFR219 and AFI 40-402, Protection of Human Subjects in Biomedical and Behavioral Research. The work reported herein was performed under the United States Air Force Surgeon General-approved Clinical Investigation No.C.2003.097

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Table 1

Analysis of Variance for Pain Threshold, Pain Tolerance and Pain Intensity

		Sum of Squares	*df*	Mean Square	*F*	Sig
Pain Threshold	Between Groups	1158.682	2	579.341	5.674	.009
	Within Groups	2654.907	26	102.112		
	Total	3813.590	28			
Pain Tolerance	Between Groups	40880.531	2	20440.266	3.020	.066
	Within Groups	175991.611	26	6768.908		
	Total	216872.142	28			
Pain Intensity	Between Groups	879.346	2	439.673	1.212	.314
	Within Groups	9434.619	26	362.793		
	Total	10311.966	28			

Table 2

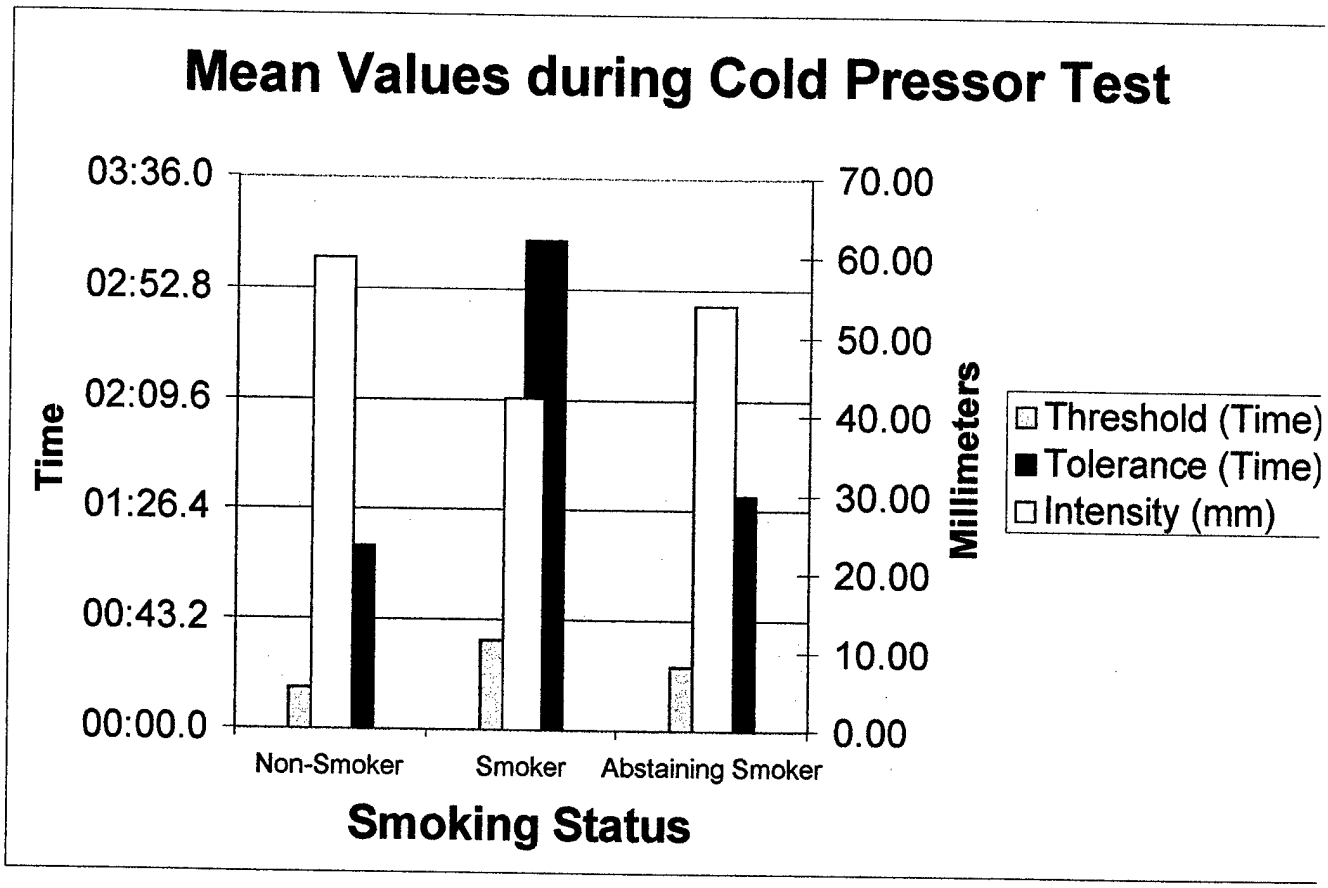
Tukey HSD Post Hoc Analysis: Dependent Variable Pain Threshold

(I) Smoking Status	(J) Smoking Status	Mean Difference (I-J)	Std. Error	Sig	95% Confidence Interval	
					Lower Bound	Upper Bound
Non-smoker	Smoker	-0:00:19.19	0:00:06.24	.013	-0:00:34.69	-0:00:03.70
	Abstaining Smoker	-0:00:09.20	0:00:05.03	.180	-0:00:21.70	-0:00:03.29
Smoker	Non-smoker	0:00:19.19	0:00:06.24	.013	0:00:03.70	0:00:34.69
	Abstaining Smoker	0:00:09.99	0:00:07.38	.379	-0:00:08.35	0:00:28.33
Abstaining Smoker	Non-Smoker	0:00:09.20	0:00:05.03	.180	-0:00:03.29	0:00:21.70
	Smoker	-0:00:09.99	0:00:07.38	.379	-0:00:28.33	0:00:08.35

Figure Captions

Figure 1. Mean scores during cold pressor test

Figure 1


Mean Values during Cold Pressor Test
03:36.0
02:52.8
02:09.6
01:26.4
00:43.2
00:00.0
Time
70.00
60.00
50.00
40.00
30.00
20.00
10.00
0.00
Millimeters
Threshold (Time)
Tolerance (Time)
Intensity (mm)
Non-Smoker
Smoker
Abstaining Smoker
Smoking Status