Retrospective Review

Cigarette Smokers Have Reduced Risk for Post-Dural Puncture Headache

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Background: Although headache is the most common complication of dural puncture, knowledge gaps remain about patient-related risks. Data are lacking on the role, if any, of tobacco smoking, race, anxiety, depression, and Post Traumatic Stress Disorder (PTSD) in conferring risk for post-dural puncture headache (PDPH).

Objective: To determine the influence of tobacco smoking, race, anxiety, depressed mood, and PTSD on the risk for PDPH.

Study Design: Retrospective chart review, single site.

Methods: We determined the incidence of significant PDPH according to age, sex, race, smoking status, and psychiatric diagnosis in 153 consecutive research patients at the Cincinnati Veterans Affairs Medical Center who had continuous cerebrospinal fluid (CSF) sampling performed after using a large-bore (17 gauge) Tuohy needle to place a 20-gauge polyamide catheter in the lumbar spinal canal.

Results: Thirty-nine subjects (25.5%) had significant PDPH, defined as requiring an epidural blood patch for therapy (an average of 4 days post-procedure). Greater age was associated with a decreased risk of PDPH ($P = 0.008$); subjects over the age of 40 had the lowest incidence (15.7%). Women and men had a 31.4% and 23.7% incidence of PDPH, respectively; these were not significantly different ($P = 0.38$). Neither were rates of PDPH in Caucasians (28.0%) and African-Americans (15.6%) significantly different ($P = 0.18$). Healthy controls had a higher incidence of PDPH than patients with PTSD ($P = 0.032$). Smokers had a lower incidence of PDPH than non-smokers, 13.7% vs. 34.1% ($P = 0.009$).

Limitations: This was not a prospective study, rather a retrospective chart review.

Conclusion: Most notably, smokers had a considerably reduced rate of PDPH in comparison with non-smokers. This information could be a useful addition to the clinical assessment of relative risk for PDPH. Further research into the mechanisms by which tobacco smoking may inhibit PDPH, such as nicotine stimulation of dopamine neurotransmission or alterations in coagulation, appears warranted.

Key words: Anxiety, cerebrospinal fluid (CSF), epidural blood patch, headache, lumbar puncture, pain, post-dural puncture headache, post-traumatic stress disorder (PTSD), race, tobacco, Tuohy needle

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Headache is the most common complication of dural puncture. A post-dural puncture headache (PDPH) typically follows cerebrospinal fluid (CSF) leakage through the dural puncture site due to delayed closure, which decreases CSF volume, pressure, or both (1,2) and has an increasing incidence and symptom severity with larger needle gauges. Neurochemical factors may also be involved in PDPH (3,4). Headache onset typically occurs within 48 hours of the procedure and most resolve

within 7 days, but some last for weeks (5,6).

While a number of clinician-controlled factors impact the rate of PDPH (2,7) (Table 1), there are many gaps in our understanding of patient-related risks. With regard to the latter, females (8), young adults aged 18 - 30 (9), and individuals with a history of chronic headache have been reported to be at increased risk for PDPH (5,7). Conversely, individuals over the age of 60 have lower risk (10). In data collected from 1949 through 1952, African-American ("colored") patients were reported to have only one-fifth the post-spinal anesthesia headache incidence of Caucasians (11). Relationship between race and PDPH has since, to our knowledge, been over-looked--or not regarded as a risk factor for PDPH (7,12). We are also not aware of any information on potential links between psychiatric syndromes or tobacco use and PDPH.

Clinically, the incidence of PDPH is quite low and has decreased with the common use of small gauge pencil-point needles. The low incidence makes new studies of PDPH risk difficult. Tuohy needles, on the other hand, are curved and somewhat blunt to prevent sheering of the spinal canal catheter that is threaded through it. The Tuohy tends to create a jagged tear in the dura and the headache rate after dural puncture by Tuohy needle is generally high, reportedly averaging 70% when a 16 ga. needle is used (13). Our use of a large-bore (17 ga.) Tuohy needle to place a 20 ga. polyamide catheter in the lumbar spinal canal, where it remains for approximately 8 hours during psychoendocrine experiments involving continuous CSF withdrawal, permits us to observe a patient population with a high incidence of PDPH and to fill some knowledge gaps concerning risks.

We reviewed the medical records of 153 consecutive research patients studied at the Cincinnati Veterans Affairs Medical Center (VAMC) who had continuous CSF sampling performed after a 17 ga. Tuohy needle was used to place a 20 ga. polyamide catheter in the lumbar spinal canal. Both military veterans and non-veterans, male and female, were studied. We determined the incidence of significant PDPH according to age, sex, race, smoking status, and psychiatric diagnosis (anxiety and depression, post-traumatic stress disorder [PTSD], or healthy volunteer). Since all subjects with post-procedure, postural headache were treated with epidural blood patch, per experimental protocol, we used epidural blood patch rate as a surrogate for significant PDPH.

Table 1. *Modifiable risk factors for PDPH.*

Needle shape
Needle size
Bevel orientation and insertion angle
Stylet replacement
Operator experience

Methods

Subjects

Computerized medical and protected research records on 153 consecutive cases of continuous CSF sampling at the Cincinnati VAMC, all for research purposes, in University of Cincinnati Medical Center Institutional Review Board- and Veterans Affairs Medical Center Research and Development Committee-approved protocols were reviewed. Of these 118 (77%) were male and 35 (23%) female. One hundred and eighteen subjects were Caucasian (77%), 32 (21%) were African-American, and 3 (2%) were biracial. Twenty percent of our subjects were between the ages of 20 and 30 years old, 26% were 30 - 39 years old, and 54% were aged 40 to 60 years old. Thirty-three percent of the total sample smoked tobacco, 56% were non-smokers (never-smokers), 10% had quit smoking, and 1% had undetermined smoking status. n the smokers, tobacco use was stopped 12 - 13 hours before commencement of CSF withdrawal. Healthy controls comprised 35% of the sample, 42% of the total group were patients with PTSD and 23% had both clinically significant anxiety and depression (see Table 2). Diagnostic criteria from the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders, 4th Edition, were used (14). Except for tobacco, all subjects were drug free, as documented by urine toxicology. Several subjects had admitted to cannabis smoking, but only one was positive in the urine drug screen. Otherwise, all subjects were medication free. Data on non-recent historical elements of marijuana smoking, such as duration, frequency, amount smoked, and last use were not collected. Among those who had taken medication, the medication-free period was a minimum of 5 disappearance time half-lives.

Dural Puncture and Cerebrospinal Fluid Sampling

Subjects were admitted to the Psychoneuroendo-

crinology Unit of the Cincinnati VAMC the day before CSF sampling. Diet, fluids, smoking, intravenous catheter placement, and activity were strictly controlled (15). Smoking was prohibited from midnight before the procedure through the morning after, when subjects were permitted to ambulate as tolerated. A 20-gauge polyamide catheter was placed in the subarachnoid space via a 17 ga. Tuohy needle between 0800 - 0830 hours as previously described (15). A total of 36 mL of CSF was continuously collected for 6 hours at a rate of 0.1 mL per minute using a peristaltic pump. Physiologic saline solution was infused at 100 mL/h throughout the procedure.

Assessment and Treatment of Post-dural Puncture Headache

All subjects who met criteria for PDPH, as outlined by the International Classification of Headache Disorders-2 (16), were offered an epidural blood patch by an anesthesiologist an average of 4 days after the procedure. All consented to this except one subject, a Jehovah Witness, who refused on religious grounds and was excluded from analysis. No other subject had a clinically significant headache or disruption of activities of daily living.

Statistical Analyses

Fisher's Exact test was used to compare incidence of PDPH for the categorical variables examined in this study: age group, race, sex, diagnosis, and tobacco use. The Wilcoxon Rank Sum test was used to compare body mass indices between the PDPH and non-PDPH groups, diagnostic groups, and tobacco vs. no-tobacco groups. For variables with more than 2 categories (diagnosis, age group) the Kruskal-Wallis test was used. Logistic regression was used to allow for multiple explanatory variables in the model where the presence or absence of PDPH was the response. Backward elimination was used to remove variables that did not have an effect on the response in the presence of the other variables remaining in the model. Variables stayed in the model if their level of significance, adjusted for the other variables in the model, was at most 0.05. All analyses were conducted using SAS® statistical software version 9.2 (The SAS® Institute, Inc., Cary, NC).

Results

In 153 continuous CSF sampling procedures, 39 subjects (25.5%) had significant headache and received an epidural blood patch (Table 2). The epidural blood patch was immediately effective in resolving the PDPH in 37 (94.9%) of subjects. The 2 other cases of PDPH resolved after a second epidural blood patch, performed 3 or 5 days after the first.

Age, Sex, Race, and Clinical Diagnosis

There was a significant difference in incidence of PDPH among the 3 age groups; subjects in their 20s had a higher rate (40.0%) than those in their 30s (35.0%) who had, in turn, a higher rate than those 40 years and over (15.7%) (Fisher's Exact $P = 0.008$).

The PDPH rate was not statistically significant different between the sexes (women 31.4%, men 23.7%;

Table 2. *Post-dural Puncture Headache Ratem, Demographics, & Diagnoses*

		Male (118)		Female (35)		Total
		PDPH		PDPH		PDPH
		23.7%		31.4%		25.5%
Race	Caucasian	96	25%	22	40.9%	28%
	A.A.	20	15%	12	16.6%	15.6%
	Bi-racial	2	50%	1	0	33.3%
Diagnosis	Control	43	32.6%	14	35.7%	33.3%
	Anx/Dep	13	38.5%	19	26.3%	31%
	PTSD	62	14.5%	2	50%	15.6%
Age	20s	29	37.9%	1	100%	40%
	30s	24	29.1%	16	43.7%	35%
	40-60	65	15.30%	18	16.6%	15.7%
Tobacco	Smoker	45	15.6%	5	0	14%

Fisher's Exact *P* = 0.38) or races (Caucasian 28.0%, African-American 15.6%; Fischer's Exact *P* = 0.18).

There was no statistically significant difference in PDPH among diagnoses (Fisher's Exact P = 0.057). Head-to-head comparisons showed that healthy controls and patients with anxiety and depression had similar PDPH rates (Fisher's Exact *P* = 1.0); however, the controls did have a higher incidence of PDPH in comparison to patients with PTSD (33.3% vs. 15.6%, Fisher's Exact *P* = 0.032). Patients with anxiety and depression, but without PTSD, had a higher incidence of PDPH (31.2%) than those with PTSD, though this difference did not reach statistical significance (Fisher's Exact *P* = 0.11).

Smoking

In the following analyses only smokers and non-smokers were considered; those who quit (10% of the sample) were omitted from further analysis. Cigarette smokers had a lower incidence of PDPH than non-smokers, 13.7% vs. 34.1%, respectively (Fisher's Exact Test *P* = 0.009). This association persisted when subjected to a variable selection procedure, using backward elimination, in a logistic regression model. Tobacco use was the only explanatory variable to survive the backward elimination process; the other variables were diagnosis, race, sex, body mass index (BMI), and age group. The odds of a non-smoker developing a PDPH were approximately 3.3 times that of smokers (*P* = 0.012, with a 95% confidence interval for the Odds Ratio of 1.3 – 8.1)

Body Mass Index

Smokers and non-smokers had similar body mass indices (27.5 ± 4.2 vs 28.6 ± 5.1 mean ± SD, respectively, *P* = 0.27). BMI was also similar in the epidural blood patch vs. non-epidural blood patch groups (*P* = 0.70), among age groups (*P* = 0.28 using the Kruskal-Wallis test), and between diagnostic groups (*P* = 0.27 using the Kruskal-Wallis test). In a direct comparison, patients with PTSD were slightly heavier than controls (BMI 28.8 ± 4.7 vs. 27.6 ± 4.9), but this finding was not statistically significant (*P* = 0.11 by Wilcoxon Rank Sum Test).

Discussion

The major finding of our study is that tobacco smokers, who constituted one-third of our patients, developed fewer PDPHs than non-smokers. Smoking engenders platelet activation (17) and changes platelet cell membrane morphology to a more "globular" appearance (18). Smokers have increased thrombogenicity, thicker, stickier, and more dense fibrin networks in clots, lower clot permeability, and less susceptibility to clot lysis (19-22). Given that incomplete sealing of the dural hole, with attendant CSF leakage, is a major pathophysiological factor in PDPH, the clot-promoting and coagulation-inducing effects of smoking may be important mechanisms whereby smokers have much lower headache rates. We cannot rule out the possibility that other tobacco smoke-related neurochemical effects might be important. For example, that nicotine stimulates central nervous system (CNS) activity of the reward-signaling neurotransmitter dopamine (23) could be significant; additionally, dopamine is converted directly into norepinephrine, whose vasoconstricting actions may also be a factor in limiting PDPH (24,25). In this regard, the antidepressant mirtazapine has a net positive effect on noradrenergic neurotransmission (26) and has been anecdotally reported to improve PDPH (25). Interestingly, however, we previously observed that smokers had low CSF concentrations of the major dopamine metabolite homovanillic acid (27). Nicotine also stimulates CNS corticotropin-releasing hormone (CRH) release (28), although, as with homovanillic acid, we observed lower CSF CRH in smokers relative to non-smokers (29). Overall, the neurobiological and biochemical effects of tobacco smoking are numerous and remain largely unclear (30-33); a review of this area is beyond the boundaries of the current report.

Our study also provides rare data on race as a potential risk factor for PDPH. In our sample, African-Americans had a lower incidence of PDPH (56% of the incidence in Caucasians), but this was not statistically significant, possibly due to the relatively small number of African-Americans in our data set (a total of 32). A PDPH study carried out 60 years ago in Fairfield, Alabama, concluded that "there was a definite preponderance of headaches in the white race" (11). Only 3 of 894 "colored patients" were reported to have developed a "post spinal headache" following spinal anesthesia, in comparison with 25 of 1,406 white patients (11). This 1954 report and our current contribution appear to contain the only available data on race as a risk factor for PDPH. While we excluded patients with sickle cell anemia, neither study screened for sickle cell trait, which could hypothetically enhance clotting at the site of dural puncture.

The well-known significant reduction in risk of PDPH with older age (2) is borne out in the current results. Our data are also consistent with the notion that "female (nonpregnant) gender may be a risk factor for the development of PDPH" (8), as a thorough meta-

analysis of gender and PDPH concluded. In our data set, women have a lower rate of PDPH than men (75% of the men's rate) but this difference was not statistically significant, possibly because of limited statistical power (only 35 subjects were female). Unlike the situation with human immunodeficiency virus seropositive patients with a BMI ≤ 25 (34), low BMI was not a significant risk factor for PDPH in our populations.

Finally, it is of interest that research subjects with war-related PTSD, but not patients with mixed anxiety and depression and without PTSD, had lower rates of PDPH than healthy volunteers (a group which included some military veterans). This result was not due to cigarette smoking in the group with PTSD, as this, and the other variables assessed, were controlled in the statistical analysis. Since patients with PTSD frequently suffer with chronic pain (35) the lower rate of PDPH in this group could be regarded as a surprise. However, all of our subjects with PTSD were in good general health with the exception of PTSD. Regardless of the reason(s) for the lower PDPH rates in patients with PTSD, it is notable that neither this cohort nor the group with mixed anxiety and depression had any more frequent PDPHs than healthy controls.

Limitation

A retrospective rather than a prospective study design and lack of quantification of tobacco exposure were limitations of this study.

Conclusion

In a mixed, medication-free research sample we found that cigarette smokers had much lower rates of PDPHs than non-smokers. In our sample, the strength of this finding is similar in significance to the decline in PDPHs with older age. This information could be clinically useful in the informed consent procedure.

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