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Chronic Pain and Hepatitis C Virus Infection in Opioid Dependent Injection Drug Users

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Abstract

It is unknown if infection with hepatitis C virus (HCV) is a risk factor for pain among persons who have used injection drugs (IDU). Multivariate regression was used to determine whether HCV was associated with greater likelihood of reporting significant chronic pain and discomfort intolerance in a cohort of 97 opioid dependent IDU. Study results suggest that participants with HCV may be more likely to suffer chronic pain (aOR=1.98; 95% CI: 0.76 to 5.12, p=0.16). Furthermore, HCV was found to be associated with a higher discomfort intolerance scale score, reflecting intolerance to physical discomfort (β=2.34; 95% CI: 0.06 to 4.62, p=0.04). Infection with HCV may be an overlooked cause for chronic pain and discomfort intolerance among opioid dependent IDU.

Keywords

Hepatitis C virus; injection drug use; chronic pain; pain hypersensitivity

Background

Chronic pain and substance use frequently co-exist for reasons that are poorly understood. Opioid dependent persons appear particularly vulnerable to chronic pain and pain hypersensitivity. There is a high prevalence of chronic severe pain (37–61%) among opioid dependent patients receiving methadone maintenance [1–3], and studies in HIV-infected populations have found that patients with a history of injection drug use (IDU) report more pain than those with no IDU. [4–8] Furthermore, experimental pain studies have demonstrated lower pain thresholds among opioid dependent persons .[9–12]

Opioid injectors are at high risk for hepatitis C virus infection (HCV). [13–16] HCV has been linked to painful conditions (peripheral neuropathies, arthritis, etc.) in a large case series of infected patients. [17] Furthermore, quality of life studies have observed greater bodily pain among HCV+ v. HCV- patients. [18] These studies suggest a high prevalence of painful conditions among HCV+ patients; however, support for this association has been limited by lack of controls and/or adjustment for important confounders, most notably substance use disorders.[19–21] Researchers have hypothesized that increased levels of inflammatory

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cytokines may provide a biologic link between HCV and fibromyalgia [22], but a large population-based study failed to support such an association. [23]

While the clinical overlap of substance use, HCV, and pain is commonly seen in medical settings, there has been little attention to HCV as a direct etiology for pain. One study of veterans seeking addiction services found that HCV seropositivity was associated with a three-fold increased risk for persistent pain.[24] HCV may be an under-recognized and potentially modifiable cause for pain for patients with substance use. This study was undertaken to examine whether reported infection with HCV was associated with chronic pain and discomfort intolerance in a sample of opioid dependent injection drug users with depressive symptoms.

Methods

Study Sample and Design

This cross-sectional study used baseline data from participants in a randomized, double-blind, placebo-controlled trial to determine whether treatment for depressive symptoms increases treatment retention among opioid dependent patients initiating office-based buprenorphine treatment. Study inclusion criteria included: age 18–65, a DSM-IV diagnosis of opioid dependence, a score on the Modified Hamilton Depression Revised Scale (MHDRS) [25] greater than 14, the absence of significant suicidal ideation, willingness and ability to complete a 3-month treatment with buprenorphine, no history of severe mental illness (bipolar disorder, schizophrenia, schizo-affective, or paranoid disorder), no currently prescribed psychotropic/antidepressant medications or medications that could cause depression (including interferons), and ability to complete the study assessment in English. Between November 2006 and May 2009, 932 individuals were screened by telephone, and of those, 394 callers appeared eligible for the study and were invited for an in-person screening visit. Of the 226 who attended this visit, 147 fully met criteria and agreed to enroll the parent study. This study restricted analyses to 97 participants who were current or former injection drug users (i.e. reported ever injecting drugs as assessed by an HIV-risk screening instrument). [26]

Pain Outcomes

Pain severity was assessed through the use of the Visual Analogue Scale (VAS), a rating scale that allows participants to mark their pain on a 100mm line that ranges from “no pain” to “worst pain imaginable”, and translates their pain to a value 0–100. [27] Pain interference was assessed using the mean of the 7-item subscale from the Brief Pain Inventory Short Form (BPI).[28] The subscale measures pain interference in different domains such as sleep, work and relationships, rating each item from “0” (pain does not interfere) to “10” (pain completely interferes). The primary outcome was significant chronic pain, defined as pain that was of at least moderate in intensity (VAS score≥40) or caused at least moderate interference (BPI interference score≥5), and which had been present for at least 6 months. This definition was modified from that used in a study by Rosenblum et. al. [3] The secondary outcome of interest was discomfort intolerance which was measured using the “Discomfort Intolerance Scale” (DIS).[29] The DIS is a 5-item scale that was designed to measure the construct of discomfort intolerance, defined as the individual’s perception of their ability to tolerate uncomfortable sensations. The scale is comprised of 5 questions (sample questions: “I am more sensitive to feeling physical discomfort compared to most people” and “I take extreme measures to avoid feeling physically uncomfortable”) of which there is a range of seven possible responses (“0” or “Not at all like me” to “6” or “Extremely like me”). Responses were analyzed as a total summed score, with higher responses indicating a lower tolerance for physical discomfort. Additional analyses used data on the reported location of

pain participants had in the previous week, which included: headache, abdominal pain, back pain, joint pain or muscle pain.

Predictors

The primary predictor of interest was chronic HCV infection defined as a positive response to the question "Do you have hepatitis C virus (HCV)?" Additional covariates were age, sex, race (white v. non-white), severe depression (score greater than 28 on the Beck Depression Inventory II [30]) and report of starting opioids for pain. Covariates were selected on the basis of face validity (demographics) or known associations with pain (depression).[31] In addition, models were adjusted for self-report of starting opioids for pain because individuals with pre-existing pain might use prescription opioids preferentially over injecting heroin, and thus be less likely to be HCV+. Initiation of opioids for pain was defined as positive response to the question: "Do you believe that you started using your primary opiate of addiction to relieve physical pain?"

Statistical Analysis

Analyses were performed used baseline study data. We examined differences in demographic and clinical variables between participants with and without reported HCV using t-tests and chi-squared tests. Multivariate logistic and linear regression were performed to determine the adjusted relative odds for significant chronic pain and the mean difference in DIS score associated with being HCV infected, respectively. Given the small sample size, a stepwise backward selection strategy was used to select a final parsimonious model using a p-value<0.2 or >10% change in the HCV coefficient as criteria for retention of covariates. Finally, prevalence of specific pain locations/types (i.e. headache, abdominal pain, back pain, joint pain and muscle pain) were compared using chi-square tests. All statistical analyses were conducted using Stata version 10.0 (College Station, TX, USA).

Results

Of the 97 participants, 37 (38%) reported that they were HCV infected; none reported being HIV infected. Participants with HCV were slightly older than those who were HCV uninfected (mean age 42 v. 37, p-value<0.01), otherwise there were no statistically significant differences between the two groups in the distribution of other variables (Table 1). The prevalence of significant chronic pain was 33% in the study cohort. A higher prevalence of significant chronic pain was observed among individuals who were self-reported HCV+ (14/37 or 38%) compared to those who were HCV- (18/60 or 30%), although this difference did not reach statistical significance (p-value=0.43). The mean DIS score was higher (indicating greater discomfort intolerance) among HCV+ compared with HCV- (19 v. 16, p=0.05). After adjusting for other covariates, participants with HCV appeared to have a nearly 2-fold increased risk for significant chronic pain, although results did not reach statistical significance at the p<0.05 level (Table 2). Participants with HCV scored significantly higher on the DIS scale, indicating a greater intolerance to discomfort (Table 3). Among those who endorsed chronic pain, there were no statistically significant differences at the p<0.05 level between reported HCV+ and HCV- participants in the prevalence of pain in the following locations: headache (29 v. 17%, p=0.42) abdominal pain (14 v. 0%, p=0.10), back pain (64 v. 61%, p=0.85), joint pain (50 v. 56%, p=0.76), and muscle pain (36 v. 28%, p=0.63).

Discussion

Among a cohort of opioid dependent injection drug users, we observed that reported HCV infection was associated with intolerance for discomfort. In addition, there was a moderately

strong (albeit non-significant) association between HCV and significant chronic pain. Although patients with HCV have been observed to have a high prevalence of painful conditions [20–22], this is the first study to find an independent association between HCV and pain in a cohort of IDU.

HCV may be associated with chronic pain in IDU through a number of different mechanisms. First, it may result in hepatic and non-hepatic complications that cause pain.[17] Our study observed the prevalence of pain to be higher in multiple domains (headache, abdominal pain, muscle pain) among participants with HCV. Second, HCV is associated with depression[32] which is a strong risk factor for pain.[31] However, given that the association between HCV and chronic pain was observed even after adjustment for severe depression (and the sample itself was restricted to IDU with depressive symptoms), this appears not to be the sole mechanism. Finally, it is possible HCV may cause pain intolerance and hypersensitivity through a cytokine-mediated pathway.[22,24] Inflammatory cytokines such as TNF-α and interleukin-6 (IL-6) have recently been implicated in the pathogenesis of centrally mediated pain[33,34], and patients with HCV have been observed to have increased levels of these cytokines.[35–41] Our finding that subjects with HCV reported greater intolerance to physical discomfort may provide some indirect support for this hypothesis, though further experimental studies on pain tolerance thresholds are needed.

This study has major limitations, and results should be considered exploratory in nature. There was likely misclassification of our main predictor, as HCV status was based on self report rather than HCV antibody or viral load testing. Data from a prior research study suggests that self-report of HCV has good specificity (88%), but low sensitivity (77%). [42] However the relatively low HCV prevalence among persons with a history of IDU (38%) suggests that there was substantial under-reporting. This misclassification, if non-differential with regards to pain, should bias to the null which would give greater strength to our findings. However, it is also possible that patients with pain might be more routinely screened for HCV (because of increased health service use), which could bias our results. Finally, the cross-sectional nature of this study precludes inferences on causality. It is possible that seeking pain relief could cause riskier injecting behaviors that led to HCV infection rather than the opposite (i.e. HCV leading to pain). However, we are not aware of any prior research suggesting an association between pain and riskier injecting behaviors.

In summary, this study provides preliminary results suggesting that HCV is associated with chronic pain and intolerance to physical discomfort in opioid dependent IDU. Although the findings of this study are preliminary, they have important implications for clinical practice, as chronic HCV may be an overlooked and potentially treatable cause for pain among current and former IDU. More research is needed to understand how chronic viral infections such as HCV impact risk for chronic pain in substance users in order to inform future interventions.

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Table 1

Characteristics of Opioid Dependent Injection Drug Users with and without HCV

	HCV− (n=60) Number (%) or Mean (±SD)	HCV+ (n=37) Number (%) or Mean (±SD)	p-value
Age	37 (±10)	42 (±9)	<0.01
Female	11 (18)	6 (16)	0.79
Non-white	13 (22)	8 (22)	0.99
Severe Depression	27 (45)	18 (49)	0.73
Started Opioids for Pain	19 (32)	7 (19)	0.17

Table 2

Adjusted Relative Odds for Significant Chronic Pain Associated with HCV in Opioid Dependent Injection Drug Users (n=97)

	Full Model			Final Model		
	OR	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
HCV	**1.98**	**(0.72 to 5.43)**	**0.18**	**1.98**	**(0.76 to 5.12)**	**0.16**
Age	1	(0.95 to 1.05)	0.94			
Female	0.75	(0.21 to 2.68)	0.66			
Nonwhite	1.26	(0.43 to 3.69)	0.67			
Severe depression	2.31	(0.87 to 6.19)	0.09	2.35	(0.89 to 6.24)	0.09
Initiated opioids for pain	4.31	(1.49 to 12.50)	<0.01	4.5	(1.6 to 12.67)	<0.01

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Table 3

Adjusted Mean Difference in DIS Score Associated with HCV in Opioid Dependent Injection Drug Users (n=97)

	Full Model			Final Model		
	β	**95% CI**	**p -value**	**β**	**95% CI**	**p -value**
HCV	**2.31**	**(−0.19 to 4.80)**	**0.07**	**2.34**	**(0.06 to 4.62)**	**0.04**
Age	−0.02	(−0.14 to 0.11)	0.77			
Female	2.23	(−0.79 to 5.25)	0.15	2.38	(−0.54 to 5.29)	0.11
Nonwhite	−0.26	(−3.01 to 2.49)	0.85			
Severe depression	0.49	(−1.89 to 2.86)	0.68			
Initiated opioids for pain	−0.56	(−3.15 to 2.04)	0.67			