Title
Chronic Opioids and Sleep Disordered Breathing.

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Abstract

Prescription opioid use for chronic pain has increased significantly in the past several decades, and an understanding of the risks associated with long term opioid use is important for the health of the patients. Past research has suggested a link between chronic opioid use and sleep apnea, which could have a significant effect on the morbidity and mortality of the chronic pain population. The goal of this study was to determine the prevalence of sleep apnea in the chronic pain population at the UCSD Center for Pain Medicine and Palliative Care Clinic, and to determine whether treatment of sleep apnea in patients with chronic pain has an positive effect on their pain levels.

Introduction

Chronic pain is a common condition, with a prevalence of 2% to 50% depending on the population studied[5]. The impact of chronic pain in the community is significant, both for the patient and for the economic burden associated with its treatment[9]. Prescription opioid use has increased significantly in the past several decades, in response to the increased awareness of chronic pain and its effects on patient's lives. Medical use of morphine increased 73%, and oxycodone use increased 402% over a 5 year period between 1997 and 2002 [4]. As the amount of opioid use has increased, the number of unintentional deaths associated with their use has also increased. A study in Utah showed that unintentional deaths associated with opioid use has increased substantially; methadone-related deaths have increased more than 1000% from the period of 1991-1998 to 1999-2003[6]. This increase in unintentional death associated with opioid use is unsettling, and it is important to identify the risks that may be contributing to these deaths, in order to optimize treatment for patients with chronic opioid therapy.

Sleep apnea, a sleep disorder characterized by abnormal pauses in breathing, is a major health concern in the United States and worldwide. Sleep apnea can be subdivided into obstructive and central sleep apneas. Obstructive sleep apnea is characterized by episodes of upper airway obstruction during sleep, while central sleep apnea is characterized by a decrease in respiratory drive during sleep[11]. The prevalence of obstructive sleep apnea in the general population is difficult to estimate, and has varied from 3-28%. In patients greater than 65 the rate increases to between 32-42%. Approximately 5% of patients greater than 65 have central sleep apnea[16]. The known risk factors for obstructive sleep apnea include age, weight, neck circumference, alcohol, and smoking[16]. The known risk factors for central sleep apnea include age, gender, congestive heart failure, and stroke[2]. Sleep apnea can have profound effects on quality of life, including increased incidence of motor vehicle crashes, increased daytime sleepiness. It is also associated with cardiovascular disease and reduced neurocognitive function[1].

Research has been done to address whether opioid use may be associated with an increased prevalence of sleep apnea. Mu-receptors are known to be involved in both the control of respiration and sleep cycles, and the receptors are present in the central and peripheral nervous systems. It is a well known clinical finding that acute opioid administration can cause sedation and respiratory depression[13]. Not surprisingly, acute opioid administration has also been shown to induce and exacerbate central and obstructive sleep apnea[8]. The chronic administration of opioids is known to lead to tolerance of side effects[13], and so it has been assumed in the past that as patients become less sedated, their respiratory depression also resolves. However, recent studies have shown evidence that chronic opioid use can continue to induce sleep disordered breathing[14, 12, 15]. In a study of patients receiving methadone maintenance treatment for heroin

addiction, 30% of patients were shown to have central sleep apnea[14]. A retrospective cohort study examined patients who were referred for suspected sleep apnea and found that patients who had been taking opioid medication for greater than 6 months were associated with a higher apnea-hypopnea index (AHI) and central apnea index when compared with non-opioid control patients who were matched for age, sex and body mass index[12].

An approach to treatment for chronic opioid patients who have sleep apnea has not been developed. Chronic opioid patients demonstrate a complex pattern of sleep disordered breathing which consists of both central sleep apnea and ataxic breathing, often also including signs of obstructive sleep apnea[12]. Due to the mixed etiology of the apnea, treatment with continuous positive airway pressure (CPAP) may not be sufficient. Adaptive servoventilation (ASV) is a treatment approach that was developed for patients with central sleep apnea[10]. However, ASV was not specifically designed for treatment of opioid induced breathing disturbances. A retrospective analysis of 22 patients who had been using opioid medications for at least 6 months and were being treated for sleep apnea found ASV to be insufficient therapy for their sleep disordered breathing[3]. Javaheri et al. conducted a prospective study of 5 chronic opioid patients with similar risk factors for sleep apnea. The average baseline AHI was 70/hr and CPAP therapy was only able to lower the AHI to 55/hr. Adaptive pressure support servoventilation successfully lowered the AHI to 13/h, with a central apnea index of 0/h, indicating that ASV may have potential as a treatment for sleep apnea in the chronic opioid using patient population[7].

On review of the currently published literature it is clear that more work needs to be done to address the effectiveness of sleep apnea treatment in the chronic opioid patient population. Specifically, only one prospective study has been done, which evaluated 5 patients[7]. In addition, there have been no prospective evaluations of subjects who are chronically treated with opioid

medications and have no other risk factors for sleep apnea. Furthermore, studies have not addressed whether successful treatment of sleep apnea in chronic opioid patients has a positive effect on patient's pain. Our study aims to add to the current literature by identifying the prevalence of sleep apnea in a novel patient population at the UCSD Center for Pain Medicine and Palliative Care Clinic, and by addressing whether treatment with auto-titrating positive airway pressure has a positive effect on patient's pain scores.

Definitions

The goals of this project are to determine the prevalence of sleep apnea in the chronic opioid therapy population at the UCSD Center for Pain Medicine and Palliative Care Clinic. In addition, the study will be addressing the effectiveness of APAP as a treatment for sleep apnea in the chronic opioid therapy population. This study is innovative because little research has been done to address treatment of sleep apnea in patients on chronic opioid therapy, and whether successful treatment positively affects their overall level of health. The student's role in this project will be in recruiting and training patients at the UCSD Center for Pain Medicine and Palliative Care. Furthermore, the student will also be involved in the entry, management and analyzation of the data collected in the pre-treatment evaluation, the ApneaLink device and the post-treatment evaluations. The project is expecting to enroll 20 or more patients, and will span 3 months. It is possible that the study may continue past graduation of the student. If that is the case, the ISP report will be written based on the student's time on the project and the data available before graduation.

Methods

Patients were enrolled at the UCSD Center for Pain Medicine and Palliative Care Clinic. Subjects were patients who are being treated for non-malignant pain with chronic opioid therapy.

Chronic opioid therapy was defined as a minimum of 6 months of daily opioid therapy. Doses were stable, defined as no change in morphine equivalent dose within a minimum of 1 month of study. Subjects were pre-screened for medical comorbidities, tiredness, fatigue and depression. Subjects demographics collected included: Age, gender, race, body mass index (BMI), neck circumference, disease history, primary pain diagnosis, average pain score, daily morphine equivalent, specific opioid (long and short acting), length of time at current dose, other medications. Subjects were also screened for obstructive sleep apnea using S.T.O.P. (Snoring, Tiredness/fatigue, Observed stop in breathing, high blood pressure) and B.A.N.G. (BMI > 35 kg/m2, Age >50y, Neck circumference >40cm, Gender male) questionnaires. Patients were also screened for depression, fatigue, sleepiness, and cognition using the Beck Depression Inventory, Fatigue Severity Scale, and the Mini Mental State Exam respectively. Patients who were previously diagnosed with sleep apnea were noted, but not included in the study.

Subjects were evaluated for sleep apnea using a multi-channel home sleep test (ApneaLinkPlus). Subjects were instructed in the clinic on the proper use of the device, and the subjects returned the device after using it for one night. An AHI of 5 with medical comorbidities associated with sleep apnea, or 15 without any medical comorbidities was used to identify subjects with sleep apnea. Patients that were identified with sleep apnea were referred to the Sleep Center at UCSD to discuss treatment. Successful treatment will be defined as use for more than 50% of sleeping hours, and subject tolerability of treatment will be determined using the frequency and duration of use, as reported by the subject. Subject demographics, depression, fatigue, sleepiness and cognition will be re-collected after the initiation of treatment.

Results

A total of 58 patients met initial criteria based on their chronic pain regimen to be included in the study. Of those 58, 22 patients declined to be included in the study. An additional 14 patients were previously diagnosed with sleep apnea and were receiving therapy. 22 patients were recruited, and 17 patients had returned the home sleep test by the conclusion of the study period. The study is ongoing, and more patients will be recruited in the future.

The demographic data of the 17 patients with completed studies are shown in Table 1. Of note; 82% of study participants were female and the average age was 61. The average BMI and Neck circumference were 29.3 and 36 cm respectively. 8 participants were identified as high risk for sleep apnea, using the Stop-Bang questionnaire. The average fatigue severity score of the study participants was 4.7. The average morphine-equivalent dose for their daily narcotic regimen was 210 mg.

Of the 17 patients with a completed sleep test, 7 patients were found to have an AHI greater than or equal to 5 with comorbidities, or 15 without comorbidities (Table 2, patients 1-7). These patients were referred to the sleep center at UCSD and are currently either awaiting an appointment or are in the process of evaluation for treatment. This is a prevalence of 41% in our study. The prevalence increases to 68% if the patients who were previously diagnosed with sleep apnea and currently on therapy are included. Of the study participants who had a positive AHI approximately 70% were identified in the pre-study questionnaire as having a high risk of sleep apnea (Determined by the Stop-Bang assessment), compared to 30% of patients who had a normal AHI.

Patient Number	Sex	Age	BMI	Neck[1] (cm)	MME[2] Score	BDI[3]	FSS[4]	StopBang[5]	MED[6] (mg)
1	F	72	22.8	35	30	5	5.8	Low	566
2	M	81	21.4	41	30	13	3.8	High	40
3	F	57	32.8	33	30	12	5.7	High	172.5
4	F	68	32.2	34	29	19	4.3	High	60
5	F	48	40	41	30	12	1.7	Low	328
6	M	56	29	44	30	32	6.6	High	760
7	F	71	30.6	33.5	28	19	5.9	High	40
8	F	58	20.5	34.5	29	11	4.9	Low	412.5
9	M	54	30.1	43.8	30	30	6.4	High	90
10	F	70	32.9	36	29	18	5.7	High	20
11	F	49	29.1	37	30	9	2.7	Low	120
12	F	64	29.6	38.5	30	36	7	High	228
13	F	44	47.8	38	28	25	5.4	Low	300
14	F	54	28.2	33	29	22	3.9	Low	56.25
15	F	64	21	30	28	8	3.1	Low	67.5
16	F	65	20.5	31	30	8	4	Low	225
17	F	65	29.6	32	30	14	3	Low	202.5

Table 1: Demographic data and pre-study screening results of patients

[1]Neck Circumference
[2]Mini mental status examination, scored 0 - 30
[3]Beck Depression Inventory, scored 0 - 63
[4]Fatigue Severity Score, average of 7 questions (scored 0 - 7 each)
[5]Stop-Bang Questionnaire, 8 questions. High risk defined as yes to three or more items.
[6]Morphine-Equivalent Dose

Patient Number	AHI
1	56
2	50
3	19
4	27
5	48
6	20
7	5
8	8
9	4
10	1
11	1
12	1
13	2
14	4
15	0
16	9
17	1

Table 2: Apnea-Hypopnea Index (AHI) of patients

Discussion

The prevalence of sleep apnea (defined by AHI parameters as discussed above) in this study was determined to be 41% (21.6 - 64%, 95% CI). Within the general population the prevalence of sleep apnea has been estimated to be between 3-28%[16], however studies can vary considerably in the methodology and participant data. One particular study in Spain by Duran et al., estimated a prevalence of 26-28% (20-35%, 95% CI) in people aged 30-70, with an N of 400[17]. If we compare our prevalence data to that study, we have a difference of 14% +/- 24% (95% CI). This would indicate there is no statistical difference between the prevalence data, though this is likely limited by the small number in our study. For a statistically significant difference between prevalence data, our study would require an n of 53.

When looking at the prevalence of sleep apnea in our population sample, there are some interesting epidemiological factors to point out. The average BMI in our population was 30, while many studies of the entire population estimate an average BMI of 25-28 when calculating prevalence data[16]. This would predict a higher prevalence of sleep apnea within our population regardless of their chronic opioid usage. Conversely, our study population was 82% female which would predict a lower prevalence of AHI, given the increased risk in the male population.

The average morphine-equivalent dose (MED) in patients who had a positive AHI was 281 mg/day, compared to 172 mg/day in those who did not. The difference between these two means, however, is not statistically significant (two-tailed P value of 0.2977). A larger sample size would be needed to determine whether there is a significant difference in the average narcotic dose of patients with a positive AHI.

In addition to the small number of patients recruited into the study, the design of the study also had a number of limitations which may have contributed confounding factors when estimating prevalence data. The study was unable to offer a monetary incentive for inclusion in the study, which may have had an effect on the kinds of patients who were enrolled in the study. It is reasonable to imagine that if a patient felt like they had sleep apnea (either due to fatigue, or they knew they snored), they would have been more likely to consent to the study since there was something for them to gain. In patients who did not have signs suggesting sleep apnea, they would see little incentive in being involved in the study. This may have artificially increased the prevalence in our study population. Similarly, patients were required to return the sleep devices within a reasonable amount of time. This may have contributed to an overall higher socioeconomic status of the patient population, when compared to the general population, because of factors such as time to return the device, as well as the price of gasoline involved in making a second trip to clinic to return the device. Lastly, while we know the number of patients who met initial criteria that were already diagnosed with sleep apnea and on treatment, we cannot use their data in this study as they were not consented for the study. This lowers the prevalence calculated, as we are excluding patients on chronic opioids who have sleep apnea

Conclusion

Prescription opioid use for chronic pain has increased significantly in the past several decades, and an understanding of the risks associated with long term opioid use is important for the health of the patients. Past research has suggested a link between chronic opioid use and sleep apnea, which could have a significant effect on the morbidity and mortality of the chronic pain population. This pilot study of 17 patients at the UCSD Center for Pain Medicine and Palliative Care Clinic determined the prevalence of undiagnosed sleep apnea to be 41%, which is

higher than what has been estimated in the past for the general population. However, further patient recruitment would need to be done to determine whether this difference is statistically significant at larger population values. In addition, long-term follow-up is planned for those patients who undergo treatment of their sleep apnea to determine what, if any, effect treatment of sleep apnea has on their chronic opioid requirement.

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